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Please can you ensure that tracked changes are used to alter the report	We have done a "marked" version as the tracked version does not covert retaining the details of edits. We have also submitted a clean version of the report; which the CONSORT checklist is referenced to. Although we are still awaiting the authorship and declaration form from one co-author; and missing the ORCID for another, we have submitted the revision to avoid further delays

UPLOADS

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**A multicentre randomised controlled Trial of IntraVenous immunoglobulin versus standard therapy for the treatment of transverse myelitis in adults and children (STRIVE).**

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**Competing interests:** IVIG is provided by Biotest AG, Germany, and should any commercial opportunity arise, the industrial partner has an option to an exclusive license from the sponsor (Guy's and St Thomas' NHS Foundation Trust) and potential for a revenue sharing arrangement in the event of a commercial outcome; **MA** serves on the data safety monitoring board for a study sponsored by Neurim Pharmaceuticals, has received consultation fees from Novartis and is on the editorial advisory board for the International Journal of Language & Communication Disorders. **PB** has received fees for speaking and consulting from Biogen, Roche, Genzyme, Teva & Merck. **OC** serves as consultant for Novartis, Biogen and GE Healthcare and is an Associate Editor of Neurology. **GG** has received consultation and speaking fees from Biogen-Idec, GSK, Merck-Serono, Novartis, Genzyme-Sanofi and Synthon BV and is on the steering committee for studies sponsored by AbbVie, Biogen-Idec, Novartis, Teva and Roche. **JP** serves on the scientific advisory board for the Charcot Foundation and has performed advisory work for Biogen Idec, Merck Serono Ltd, Bayer Schering Pharma, Novartis Pharmaceuticals UK Ltd, Teva Pharmaceutical Industries Ltd, Gilenya, Ono Pharmaceutical Co Ltd, Primary i-research, Alexion and Chugai Pharma Europe and receives research support from the Merck Serono Ltd, Bayer Schering Pharma, Biogen Idec and Teva, and received conference expenses from Novartis, Merck Serono and Biogen Idec. **MP** has received a meeting support grant from Euroimmun. **AJ** is supported by the NHS National Specialised Commissioning Group for NMO and has been a

consultant for Shire, Alexion and Chugai and has received research funding from Biogen and Alexion. **ML** has received consultation fees from CSL Behring, travel grants from Merck Serono, and been awarded educational grants to organise meetings by Novartis, Biogen Idec, Merck Serono and Bayer. All other authors declare no competing interests.

# **1 Abstract**

## **1.1 Background**

Transverse myelitis (TM) is an immune-mediated disorder of the spinal cord affecting adults and children causing motor, sensory and autonomic dysfunction. A prolonged recovery phase which may continue for up to many years. Neuromyelitis-optica (NMO) is an uncommon relapsing inflammatory central nervous system (CNS) condition where TM can be the first presenting symptom. As TM and NMO affects many patients at the prime of their working life, the disorder can impose a significant demand on health resources. There are currently no robust controlled trials in children or adults to inform the optimal treatment of TM. However, treatment with intravenous immunoglobulin (IVIG) is being effectively used in the management of a range of neurological conditions. Although other interventions such as plasma exchange (PLEX) in addition to intravenous methylprednisolone therapy can be beneficial in TM, PLEX is costly and technically challenging to deliver in the acute setting. IVIG is more readily accessible and less costly.

## **1.2 Objective(s)**

To evaluate if additional and early treatment with IVIG is of extra benefit in TM compared to standard therapy of intravenous steroids.

## **1.3 Design**

A multicentre, single-blind, parallel-group randomised controlled trial of IVIG versus standard therapy for treatment of TM in adults and children.

## **1.4 Participants**

Patients aged 1 or over who have been diagnosed with either acute first onset transverse myelitis or first presentation of NMO. A target recruitment of 170 (85 per arm) participants.

## **1.5 Interventions**

Participants were randomised 1:1 to treatment with IV methylprednisolone only or IV methylprednisolone plus 2g/kg IVIG in divided doses within 5 days of first commencement of steroid therapy.



## **1.6 Main outcome measures**

Primary outcome measure: a two-point improvement in American Spinal Injury Association (ASIA) Impairment Scale 6-months post randomisation. Secondary and tertiary outcome measures: change in ASIA motor and sensory scores, Expanded Disability Status Scale (EDSS), health outcome, quality of life assessment, Client Services Receipt Inventory and pain, bladder and bowel data sets.

## **1.7 Results**

26 participants were screened and two randomised into the study. With the limited sample size, treatment effect could not be determined. However, we identified barriers to accrual that included; strict inclusion criteria, short enrolment window, challenges associated with the use of ASIA impairment scale as an outcome measure and estimation of the incidence of TM.

## **1.8 Limitations**

The study did not reach the end-point.

## **1.9 Conclusions**

The effect of IVIG in TM/NMO could not be determined by this study. Investigators should be aware of the potential challenges associated with carrying out rare disease trial that recruits within a small time window.

## **1.10 Future work**

The study question is one that still necessitates investigation. Preliminary work that would ameliorate the effect of the barriers encountered by this study is vital.

## **1.11 Study registration**

EudraCT (REF: 2014-002335-34), Clinicaltrials.gov (REF: NCT02398994) and ISRCTN (REF: 12127581).

### **1.12 Funding details**

National Institute for Health Research, Health Technology Assessment (project number 11/129/148); Biotest AG, Germany (supply of IVIG); and The Transverse Myelitis Society (excess research cost to facilitate study initiation).

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## 5 List of abbreviations/glossary

ADEM	Acute disseminated encephalomyelitis
AE	Adverse Event
AQP 4	Aquaporin 4
AR	Adverse Reaction
ASIA	American Spinal Injury Association
CI	Chief Investigator
CNS	Central nervous system
CRF	Case report form
CSF	Cerebrospinal fluid
CSRI	Client Services Receipt Inventory
CTU	Clinical Trials Unit
ED 5Q	Euro Quality of Life Health Questionnaire
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
ICC	Intra-cluster correlation coefficient
IME	Important Medical Event
IVIG	Intravenous immunoglobulin
IV-MP	Intravenous methylprednisolone
LMM	Linear mixed modelling
MAR	Missing at randomisation
MHRA	Medicines and Healthcare Products Regulatory Agency
NMO	Neuromyelitis optica
PedsQL	Paediatric Quality of Life Questionnaire

PI	Primary Investigator
PIS	Patient Information Sheets
PLEX	Plasma exchange
RCT	Randomised controlled trial
SAE	Serious Adverse Event
SCI QoL	Spinal Cord Injury Quality of Life Questionnaire
SmPC	Summary of product characteristics
SUR	Serious Unexpected Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TM	Transverse myelitis
UAR	Unexpected Adverse Reaction

## 6 Scientific Summary

### 6.1 Background

Transverse myelitis (TM) is a rare inflammatory disorder of the spinal cord affecting approximately 350 children and adults annually in the UK. TM attacks usually develop over 24 hours and in some cases can progress rapidly to a potentially devastating and sometimes life threatening condition. The severity of symptoms depends on the spinal cord level affected, where patients with high cervical lesions often require intensive care support to maintain respiratory function. Patients can recover fully from TM but a large number are left with significant disability. Among patients that recover, recovery occurs within weeks of onset of symptoms and is most rapid during the first 3–6 months, although further improvement may be seen up to 2–4 years.

A proportion of patients initially diagnosed with TM will subsequently relapse, often with involvement of other parts of the central nervous system, and may often be diagnosed with either multiple sclerosis (MS) or neuromyelitis optica (NMO). NMO is a relapsing subset of TM, usually caused by antibodies to aquaporin-4. Clinically, patients have recurrent episodes of predominantly myelitis and optic neuritis. Initial presentation may be with myelitis alone, making it clinically and radiologically indistinguishable from TM, and patients are thus subjected to the same acute therapeutic strategies.

There are no robust controlled trials in children or adults to inform on the optimal treatment of TM. Standard treatment with intravenous methylprednisolone (IVMP) is based on class IV evidence that it shortens relapse duration and speeds recovery in exacerbations of adult multiple sclerosis. Given the disease severity and poor outcomes, plasma exchange (PLEX) has been used in addition to standard therapy with some effect. However, PLEX is not universally available in the NHS, particularly at short notice and on weekends, and can be technically difficult and costly to administer. Randomised controlled trials have demonstrated IVIG efficacy in a number of neurological conditions. In steroid-unresponsive CNS demyelination, IVIG is often used, although supporting data are limited to small case series and single case reports. IVIG appears to inhibit complement binding, neutralise pathogenic cytokines, down regulate antibody production, enhance remyelination and modulate phagocytosis and T-cell function. The majority of these factors are common across

inflammatory disorders of the CNS including TM, providing a strong rationale for its use. The availability, ease of administration, familiarity and safety also make IVIG an attractive option in the acute setting.

## 6.2 Objective

The **primary aim** of this study was to evaluate if additional, and early, treatment with IVIG is of extra benefit in TM when compared to the current standard therapy of IVMP.

The **secondary objectives** of the study were to provide benefits whereby: -

1. The clinical and para-clinical data collected from patients will provide a robust resource and platform for other clinical studies, including identification of early predictors of poor outcome.
2. Bio banked samples from patients recruited to the study will be collected and used for carefully designed biological studies by a consortium of established basic science researchers in the field

## 6.3 Method

STRIVE study was a multicentre, single-blind, parallel-group randomised controlled trial with follow-up visits 3, 6 and 12-months following randomisation.

Patients were considered for recruitment if aged 1 or over diagnosed with either acute first onset transverse myelitis or neuromyelitis optica; with an ASIA impairment score of between American Spinal Injury Association (ASIA) Impairment Scale A through to C; and within 5 days after commencing steroid treatment.

Participants were randomised 1:1 to treatment with IV methylprednisolone alone (**control arm**) or IV methylprednisolone plus 2kg/kg IVIG in divided doses (**treatment arm**). Sample size calculation yielded a target recruitment of 170 participants, 85 participants per arm.

Primary outcome was assessed 6-month post randomisation with a good outcome defined by a two-point change in ASIA impairment scale.

Additional outcomes were measured by: -Secondary endpoint measure

1. Change in ASIA motor scale (0-100) and ASIA sensory scale (0-112) at 3, 6, and 12-months post randomisation
2. Change in Kurtzke expanded disability status scale (EDSS) measured by Neurostatus scoring at 3, 6, and 12 months
3. EQ-5D-Y for patients aged 8-12 years (at presentation) at 3,6 and 12 months
4. EQ-5D-5L for patients aged  $\geq 13$  years (at presentation) at 3, 6 and 12 months
5. Individuals  $\geq 13$  years at presentation: International SCI Quality of Life Basic Data Set at 3, 6 and 12 months
6. Client Service Receipt Inventory (CSRI) at 3, 6 and 12 months

Tertiary endpoint measure

1. International SCI Bladder/Bowel Data Set for patients aged  $\geq 13$  years at presentation to be completed at 6 and 12-months post randomisation
2. Children 2-4 years of age at presentation: Paediatric Quality of Life Inventory™ (PedsQL Parent Report for Toddlers) at 6 and 12 months
3. Children 5-7 years of age at presentation: Paediatric Quality of Life Inventory™ (PedsQL Parent Report for Young Children) at 6 and 12 months
4. Individuals  $\geq 13$  years of age at presentation: International SCI Pain Basic Data Set at 6 and 12 months

## **6.4 Results**

Of the 28 patients screened for eligibility, two participants were randomised into the study between 04/03/2015 and 08/02/2016, precluding any statistical analysis of the data and consequently any differences in treatment outcomes between the two study arms could not be determined. However, we identified multiple barriers to accrual into the study. These included; strict inclusion criteria, short enrolment window, challenges associated with the use of the ASIA impairment scale as the primary outcome measure, an inaccurate estimation of the incidence of TM severity within the target population and variability of research funding of individual sites.

## **6.5 Conclusions**

The clinical and health economic impact of the use of IVIG in addition to the standard therapy with IVMP in the treatment of adults and children with TM/NMO could not be determined by the study. As the study question is crucial to inform the acute treatment of TM/NMO patients, and thus one that necessitates further investigation, we recommend additional research to establish the incidence and the spectrum of severity of the disorder within the intended study population, alongside evaluating the utility of alternative primary outcome measures such as the ASIA motor score and other patient derived outcome measures. The success of future intervention trials in TM would be also be contingent on being able to overcome recruitment barriers identified in this study; which may have broader implications for investigators embarking on similar studies in other rare disorders.

## **6.6 Trial registration**

This study is registered with EudraCT (REF: 2014-002335-34), Clinicaltrials.gov (REF: NCT02398994) and ISRCTN (REF: 12127581).

**Word count: 1079**

## **7 Plain English Summary**

Transverse myelitis (TM) is a rare immune disorder that affects the spinal cord. Patients that develop TM can quickly lose the feeling and ability to move lower parts body (paraplegia). Additionally, the upper body can also be affected (tetraplegia). TM can affect anybody at any age and this disorder can have a significant impact both on the quality of peoples' life and demand on health resources.

Although immune treatments such as steroids, IVIG and plasma exchange are being used to treat TM, until now, no high quality trial has been conducted to measure how effective these treatments are when utilised individually or used in combination. Therefore, this randomised controlled study was designed to see if newly diagnosed TM patients would benefit from early treatment with IVIG if added to steroid therapy which we expect all patients to receive. We measured the effect of treatment using the ASIA impairment scale, an outcome measure validated in spinal injury research; and using evaluators who were not aware of treatment of patients (single blind).

After a year, despite 15 centres recruiting across the UK, only two patients were randomised. Key reasons for this include the strict inclusion criteria, short enrolment window, challenges associated with the use of the ASIA impairment scale as the primary outcome measure, an inaccurate estimation of the incidence of TM severity within the target population and inadequate funding provision for some sites. As 170 cases were required to determine a statistically significant effect of treatment, this study was closed early as this endpoint would not have been realistically achieved. However, we are now aware of important factors that need to be addressed when undertaking a trial in TM or allied rare condition.

## 8 Introduction

### 8.1 Background

Transverse myelitis (TM) is an immune-mediated disorder of the spinal cord affecting children and adults and is usually characterised by a rapid onset of paraplegia or tetraplegia, loss of sensation and sphincter disturbance.<sup>1</sup> Histologically, TM is characterised by spinal cord immune cellular infiltration, and pathogenesis is mediated by a variety of immunological mechanisms.<sup>1</sup> Attacks usually develop over 24 hours, and in some cases can progress rapidly to a potentially devastating and life threatening condition. The severity of symptoms depends on the spinal cord level affected, where patients with high cervical lesions often require intensive care support to maintain respiratory function. Patients can recover fully from TM, but a large number are left with significant disabilities. Recovery occurs within weeks of onset of symptoms and is most rapid during the first 3–6 months, although further improvement may be seen up to 2-4 years.<sup>2</sup>

Diagnostic criteria for TM were established by the TM Consortium Working Group in 2002.<sup>3</sup> A proportion of patients initially diagnosed with TM will subsequently relapse, often with involvement of other parts of the central nervous system (CNS), and may then be diagnosed with either multiple sclerosis (MS) or neuromyelitis optica (NMO). NMO is a relapsing subset of TM, caused by antibodies to aquaporin-4.<sup>4</sup> Clinically, patients have predominantly recurrent episodes of myelitis and optic neuritis. Neurodisability accrues with progressive relapses. Initial presentation may be with myelitis alone, making it clinically and radiologically indistinguishable from TM, and patients are thus subjected to the same acute therapeutic strategies

The precise numbers that make full recoveries from TM remains unclear. Studies prior to the TM Consortium Working Group criteria may have included patients with a wider range of myelopathies such as spinal cord infarction,<sup>5</sup> or may reflect the greater severity of cases seen at a tertiary referral centre such as the John's Hopkins TM Centre,<sup>6</sup> where up to 20% are reported to make a good recovery. Currently, the only report to reliably inform on the outcome of adult onset TM is a retrospective French multicentre study applying TM Consortium Working Group criteria, where 36% of patients with TM had a poor prognosis as defined by death or non-ambulating.<sup>7</sup> In children, approximately half make a good



recovery.<sup>8</sup> Hence, the majority of adults and children presenting with TM either have a fair outcome (functional and ambulatory, but with varying degrees of spasticity, urgency and/or constipation, and some sensory signs) or worse (remaining completely or largely unable to walk, having at best partial sphincter control, and being left with severe sensory deficits.<sup>2</sup> These results represent a huge burden on patients and their carer. With conservative estimates of incidence of TM in UK being 350/year (based on incidence of 3-7 per million),<sup>9,10</sup> this clearly imposes a significant cumulative demand on the health resources in the UK. Moreover, many patients are affected at peak ages that reflect their prime working life, thus resulting in loss of productivity and imposing a further financial impact on the country.

Importantly, strategies to reduce the disability in patients are urgently required, yet there are no robust controlled trials, in children or adults, to inform on its optimal treatment. The current clinical consensus is derived from data that are mainly extrapolated from Class IV evidence from case series or clinical trials for the treatment of exacerbations of adult multiple sclerosis.<sup>9-12</sup> In adults, this suggests that treatment of relapses with intravenous (IV) methylprednisolone shortens relapse duration and speeds recovery. It is from this that the current standard therapy has been based whereby, in both children and adults, treatment with high dose IV steroids is prescribed for 3-7 days to reduce inflammation, hasten recovery and restore neurological function.<sup>13</sup>

Although IV steroids are now the most common treatment for TM, there are other interventions which have proved effective in aiding recovery, but which are not routinely applied. In a retrospective analysis of 122 adults with TM, acute therapies given at one centre between 2001 and 2005 were evaluated, with the finding that some patients benefited from the addition of plasma exchange (PLEX) to IV methylprednisolone.<sup>11</sup> The efficacy of PLEX was also demonstrated in a small randomised controlled trial in adults with acute central nervous system (CNS) demyelination (including 4 patients with TM) where steroids had failed to induce a remission of symptoms.<sup>14</sup> However, administering PLEX is technically difficult and costly, making it challenging to deliver within the NHS, resulting in it not being universally available.

Treatment with intravenous Immunoglobulin (IVIG) is also used increasingly in the management of a range of neurological conditions, and its efficacy has been established clearly in randomised controlled trials for a handful of these conditions.<sup>15</sup> In adults and children with CNS demyelination who do not respond to steroids, IVIG is often used, although supporting data is limited to small case series and single case reports.<sup>16,17</sup> The most relevant actions of IVIG in the therapy of neurological diseases include: (a) inhibition of complement binding, (b) neutralization of pathogenic cytokines, (c) down-regulation of antibody production, and (d) modulation of Fc-receptor mediated phagocytosis. Additional actions include modulation of T-cell function and enhancement of re-myelination.<sup>18</sup> The majority of these factors are common across inflammatory disorders of the CNS including transverse myelopathy,<sup>19</sup> providing a strong rationale for its use in the management of TM. In addition, IVIG is cost effective when compared to PLEX and more readily accessible.

Here, we aimed to conduct a multi-centre, single blind, parallel group randomised-controlled trial to generate evidence to inform clinical and health economic decisions of IVIG use in adults and children with TM.

## **8.2 Risks and Benefits**

**Risks:** This study includes adults and children. As treatments in both arms of the trial are already used in current clinical practice, those participating will face almost no additional risk beyond what they would experience in treatment outside the trial.

**Benefits:** Interventions that can reduce the disability in patients are urgently required. The current management recommendation is largely based on expert opinion,<sup>13</sup> as there remain no robust controlled trials for the treatment of TM, in children or adults, to inform on the optimal treatment of TM. This trial seeks to evaluate if IVIG would be beneficial in the management of TM.

## **8.3 Study aim**

This multicentre, single blind, parallel group RCT was aimed at generating evidence to inform clinical and health economic decisions regarding IVIG use in adults and children with TM.

The primary objective of this single blind, parallel group randomised controlled trial was to evaluate if additional, and early, treatment with IVIG is of extra benefit in TM when compared to the current standard therapy of intravenous steroids.

In addition, our secondary objectives were to provide benefits whereby: -

1. The clinical and para-clinical data collected from patients will provide a robust resource and platform for other clinical studies, including identification of early predictors of poor outcome.
2. Bio bank samples from patients recruited to the study will be collected and used for carefully designed biological studies by a consortium of established basic science researchers in the field.

## 9 Methods and material

### 9.1 Trial Design

This was a UK multi-centre, single blind, parallel group randomised controlled trial.

Patients randomised to the **control arm** of this study were prescribed IV methylprednisolone in line with local clinical practice. Recommended dosages are as listed below: -

1. Paediatric patients will receive 30 mg/kg or 500 mg/m<sup>2</sup> capped to a maximum dose of 1 g/day for 5 days.
2. Adult patients will be given 1 gram/day for 5 days.

Patients in the **intervention arm** received the above standard therapy *plus* additional IVIG:

1. In adults, 2 g/kg will be administered in 5 divided doses
2. In children who are > 41.2kg, 2g/kg will be administered as above in adults; in children who are ≤ 41.2kg, 2g/kg will be administered in 2 divided doses

Though IVIG dosing does not need to be administered over consecutive days, it must be administered according to the dosing schedule (**Appendix 1**).

Patients may be recruited and randomised up to 5 days from the date of first commencing steroid therapy or up to 21 days from the onset of symptoms (if definitely known).

In patients who do not respond to standard IV methylprednisolone treatment or adjunctive treatment with IVIG, rescue therapy, such as PLEX, would have been instituted.

If PLEX is administered, such a therapy will attenuate treatment effect of IVIG and may indeed have a treatment effect of its own, guidance parameters were set out to define and standardise PLEX regime. Briefly:

1. Treatment failure would be considered if no improvement is seen or deterioration occurred after 14 days from presentation or 5 days after completion of either treatment arm.

2. A complete PLEX treatment would comprise of at least 5 cycles, of which in each cycle at least 75% of plasma volume is exchanged, with a 24-48-hour interval between each cycle.
3. An extra course of intravenous methylprednisolone may be given by physicians, often during the lag phase, from decision to proceed with rescue therapy to its initiation (usually 5-7days).

## **9.2 Endpoint measure**

### **9.2.1 Primary endpoint measure**

An improvement of two-points or greater on the ASIA Impairment scale (classified A-E) at 6-months post-randomisation, compared to the value measured at baseline just prior to randomisation.

### **9.2.2 Secondary endpoint measures**

1. Change in ASIA motor scale (0-100) and ASIA sensory scale (0-112) at 3, 6, and 12 months post randomisation
2. Change in Kurtzke expanded disability status scale (EDSS) measured by Neurostatus scoring at 3, 6, and 12 months
3. EQ-5D-Y for patients aged 8-12 years (at presentation) at 3,6 and 12 months
4. EQ-5D-5L for patients aged  $\geq 13$  years (at presentation) at 3, 6 and 12 months
5. Individuals  $\geq 13$  years at presentation: International SCI Quality of Life Basic Data Set at 3, 6 and 12 months
6. Client Service Receipt Inventory (CSRI) at 3, 6 and 12 months

### **9.2.3 Tertiary endpoint measures**

1. International SCI Bladder/Bowel Data Set for patients aged  $\geq 13$  years at presentation to be completed at 6 and 12-months post randomisation
2. Children 2-4 years of age at presentation: Paediatric Quality of Life Inventory™ (PedsQL Parent Report for Toddlers) at 6 and 12 months
3. Children 5-7 years of age at presentation: Paediatric Quality of Life Inventory™ (PedsQL Parent Report for Young Children) at 6 and 12 months

4. Individuals  $\geq 13$  years of age at presentation: International SCI Pain Basic Data Set at 6 and 12 months

The overall flow of study participants from admission through to randomisation and final visit is summarised in **Figure 1**.

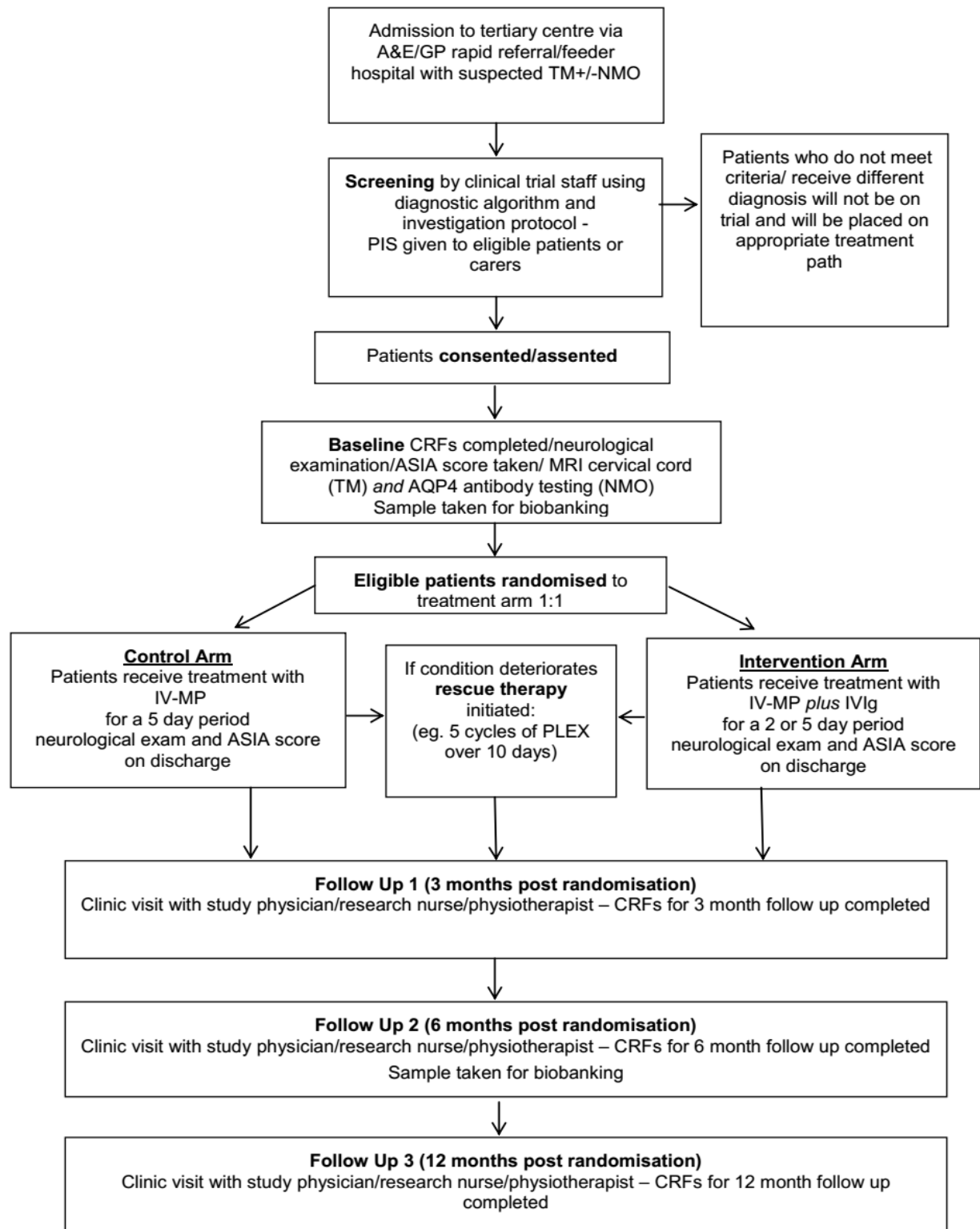


Figure 1. STRIVE participant flow chart

### **9.3 Study Subjects**

Participants were individuals who met the eligibility criteria and diagnostic algorithm (**Appendix 2**) and present to the catchment area of participating tertiary neurology centres (though neurologists may also recruit patients at district general hospitals or from rapid GP referrals). Eligibility for the study will be determined by the following criteria: -

#### **9.3.1 Inclusion Criteria**

Patients were eligible for inclusion in the trial if on presentation they:



- ii. Spinal cord MRI with contiguous T2-weighted signal abnormality extending over three or more vertebral segments, indicating a relatively large lesion in the spinal cord
- iii. Aquaporin 4 seropositive status)

### 9.3.3 Sample size

In recognition of TM as a rare condition, the power analysis took into account the inclusion of a futility analysis to be undertaken after recruitment of one third of the target sample. We assumed that the proportion of participants showing a 2-point improvement (or greater) on the ASIA Impairment scale will be approximately 0.5 (50%) in the control arm and a minimum of 0.75 (75%) in the intervention arm. The sample size calculation was based on the conservative assumption of no correlation between repeated measures.

Randomised 1:1, the primary ITT analyses will compare 76 treatment and 76 control patients, on the ASIA classification scale at 6-months post randomisation. Based on comparing the difference in the number of successes among treatment and controls the SAS sample size – chi procedure examines all 772 possible trial outcomes under the null and alternative hypotheses. The possible outcomes are then arranged in descending order and cumulative probabilities for every possible value from 76 to -76 are computed. Using a critical value that maintains the tail probability at .02355 under the null the probability under the alternative is 0.9034. The study thus had 90% power for a two-tailed test with  $\alpha=0.05$ .

The sample size was inflated for attrition, based on our experience and the design in place to minimise any loss to follow up, we estimated 10% attrition. This would require recruiting a sample size of  $(n=152/0.90) = 170$  (85 participants per arm).

The ASIA total motor score (0-100) was a secondary outcome. There is little evidence in acute transverse myelitis to summarise this in terms of variance, mean and correlation. Stata sampsi indicates that using ANCOVA, with a baseline to endpoint correlation of 0.6, there will be 87% power to detect a difference between the control and treatment arms of a medium to large effect size of 0.4. Such a difference will be of clinical significance.

### 9.3.4 Randomisation

Treatment allocation will be stratified at randomisation, by service type (adult or child) using stratified block randomisation; the block will randomly vary in size. Treatment allocation will be at a ratio of 1:1.

#### **9.3.5 Withdrawal**

The patient, or their parent/guardian, had the right to withdraw from the study at any time for any reason. The investigator also had the right to withdraw patients from the study drug in the event of inter-current illness, AEs, SAEs, and SUSARs, subsequent evidence of a different aetiology, protocol violations, cure, administrative or other reasons. Participants who either wished to or must discontinue study medication would be returned to standard care through their supervising physician, but will continue to provide study specific data at follow up visits at 3, 6 and 12 months. It was understood that an excessive rate of withdrawals can jeopardise randomisation outcomes and render the study results uninterpretable; therefore, unnecessary withdrawal of patients was avoided. Should a patient had decided to withdraw from the study, all efforts would have been made to report the reason for withdrawal as thoroughly as possible.

### **9.4 Study data**

The study data was managed as previously described in the published STRIVE protocol.<sup>21</sup>

#### **9.4.1 Data management**

Data was managed using the InferMed MACRO database system. An electronic case report form (eCRF) was created using the InferMed Macro system. This system is regulatory compliant (GCP, 21CFR11, EC Clinical Trial Directive). The eCRF was created in collaboration with the trial statisticians and the chief investigator (CI) and maintained by the King's Clinical Trials Unit. It was hosted on a secure dedicated server within KCL and source data was entered by authorised staff onto the eCRF with a full audit trail.

#### **9.4.2 Database passwords**

Database access was strictly restricted through passwords to the authorised research team. The CI or site delegate requested access from the KCTU. If a new staff member joined the study, a personalised username and password was requested via the CI or delegate.

#### **9.4.3 Identifiable data**

All participant contact information data was stored within the recruiting NHS site, which will have restricted access from password protected computers. Accrual data uploaded to the UKCRN portfolio database was anonymised and collated by the CI or Trial manager to the

CLRN. No identifiable data was entered on the eCRF or transferred to the KCTU. Participants were identified on the study database using a unique code and initials. Each investigator maintained accurate patient records detailing observations on each patient enrolled.

### **9.5 Investigational medicinal product**

Investigational medicinal product (IMP) was provided as human normal immunoglobulin (Intratect®) 100g/l solution for infusion in single 5g (50ml) or 10g (100ml) glass vial. Biotest Pharma GmbH, marketing authorisation holder of Intratect®, provided the commercially available Intratect® for use.

Annex 13 clinical trial labelling exemption was in place and approved by the Medicines and Healthcare Products Regulatory Agency (MHRA) for this trial. A standard pharmacy dispensing label was applied to the IMP at the point of dispensing by pharmacy at each investigator site.

IMP was stored in a secure area with limited access. Site pharmacies were responsible for the safe and appropriate storage of IMP at their site in accordance with manufacturers' instructions (as described below).

Intratect® storage conditions in accordance with manufacturers' instructions:

Note that IV methylprednisolone (as sodium succinate) was classed as non-investigational medicinal product in this trial and was dispensed by hospital pharmacies in accordance with their standard clinical practice.

#### **9.5.2 Risks**

The current risks associated with the Intratect® immunoglobulin are detailed in the Intratect® Summary of Products Characteristics (SmPC) which can be found at <https://www.medicines.org.uk>. A summary of these risks are provided in **Appendix 3**.

#### **9.5.3 Compliance**

Treatment with the IMP was administered under the supervision of the investigator and in a controlled clinical environment. Therefore, full patient compliance with treatment was anticipated.

#### **9.5.4 Concomitant Medication**

Only relevant immuno-modulatory medications were recorded throughout the study.

In patients who do not respond to control treatment or adjunctive treatment with IVIG, rescue therapy will be instituted in accordance with local guidelines. In most cases the rescue therapy of choice will be PLEX therapy. This will also be recorded as a concomitant medication.

#### **9.5.5 Confidentiality**

The study staff ensured that the participants' anonymity was maintained, identifying patients by their PIN numbers and initials only. The study complied with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

### **9.6 Trial sites and study duration**

The study was conducted across 15 clinical sites within the UK, with the addition of a single site that acted as a participant information centre (PIC). The first of the 15 sites was opened for recruitment on 04/03/2015, whilst the final site received its approval to commence recruiting on 08/02/2016. Recruitment was terminated early across all the 15 recruiting sites and the single participant identification centre on 11/03/2016.

## 9.7 Trial procedure

For every time point in the study, a number of questionnaires/ exam forms and assessments was carried out, as summarised in **Table 1**. Some of the questionnaires were specific to particular age groups, with age on presentation being used.

**Table 1. A summary of the STRIVE study visit schedule and associated assessments**

Schedule Time point (T)	T0 (Screening, baseline and pre-diagnosis tests)	T1 (Treatment and discharge)		T2 3M	T3 6M	T4 12M	Ongoing
		*Rescue therapy	Discharge				
Screening with diagnostic algorithm & core investigations including physical exam	x						
Patient information and informed consent	x						
Eligibility form	x						
Registration form	x						
Pre-diagnosis Tests – e.g. MRI & AQP4	x						
Randomisation	x						
Biobank samples	x				x		
ASIA Impairment Score (A-E)	x	x	x	x	P	x	
ASIA Motor and Sensory Score	x	x	x	x	S	x	
Neurostatus scoring (Kurtzke functional systems and EDSS)	x		x	x	S	x	
8-12 yrs EQ-5D-Y Questionnaire	x			x	S	x	
≥13 yrs EQ-5D-5L Questionnaire	x			x	S	x	
CSRI Questionnaire†				x	S	x	
≥13 yrs SCI QoL Basic dataset†				x	S	x	
≥13 yrs SCI Bladder Basic dataset					T	x	

≥13 yrs SCI Bowel Basic dataset					<b>T</b>	<b>x</b>	
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Schedule Time point (T)	<b>T0</b> (Screening, baseline and pre-diagnosis tests)	<b>T1</b> (Treatment and discharge)		<b>T2</b> 3M	<b>T3</b> 6M	<b>T4</b> 12M	Ongoing
		*Rescue therapy	Discharge				
≥13 yrs SCI Pain Basic dataset†					<b>T</b>	<b>x</b>	
5-7 yrs Peds QL Questionnaire†					<b>T</b>	<b>x</b>	
2-4 yrs Peds QL Questionnaire†					<b>T</b>	<b>x</b>	
Treatment form			<b>x</b>				
Concomitant medications							<b>x</b>
Discharge form			<b>x</b>				
*Rescue therapy form (if needed)		<b>x</b>					
*Relapse form (at any time point if needed)			<b>x</b>	<b>x</b>	<b>x</b>	<b>x</b>	
Adverse events							<b>x</b>
Study Status Form				<b>x</b>	<b>x</b>	<b>x</b>	
*Withdrawal form (at any time point)							<b>x</b>

**P** = primary outcome **S** = secondary outcome **T** = tertiary outcome



#### 9.7.1 Blinding

Due to the technical challenges of masking IVIG from saline, the need for rapid recruitment and the fact that follow-up will be many months after the event using objective well-defined clinical endpoints; treatment will not be blinded (no placebo). The trial manager, pharmacy, and those administering treatment are not blinded; whilst staff carrying out primary outcome assessments at follow-up and statistical analyses will be blinded to intervention.

Screening, baseline and discharge assessments were carried out in the tertiary centres by a study physician/research nurse. Following discharge from treatment in hospital, all primary outcome assessments at follow up in clinic at the tertiary centre or appropriate neurology centre, were carried out by a study physician/research nurse/physiotherapist who has been blinded to treatment. For consistency, wherever possible, the same blinded assessor was required to out the assessments at each time point. Although not mandatory secondary and tertiary outcome assessments were to be performed by a blinded member of staff at follow-up wherever possible.

#### 9.7.2 Laboratory Tests

All consenting patients had samples taken for clinical investigations and biobanking, at baseline and at the 6 month follow up. In cases, where samples for clinical investigations were already taken prior to consent, any left-over material will be used for biobanking. No additional samples will be collected unless there is a clinical indication to do so. Samples for biobanking will consist of CSF via lumbar puncture, and blood taken by venepuncture for serum, plasma, DNA, Peripheral Blood Mononuclear cells (PBMC) and RNA (site dependent), and will be stored in one of the two biobanks (London or Cardiff). These samples did not form part of this trial, but were for further hypothesis driven biological research, directed by Neil Robertson and Gavin Giovannoni (adults) and Ming Lim (paediatrics).

#### 9.7.3 MRI Sequences

As part of the routine diagnostic process for TM/NMO, brain and spinal cord sequences were acquired where possible, the results, of which was used in the study's diagnostic algorithm at screening and if the patient entered the trial, was recorded as study data.

Local protocols were in place for the acquisition of MRI sequences, which would usually include gadolinium enhanced sequences in the event of a suspected TM/NMO.

To facilitate systematic accrual of neuroimaging information it was recommended that reports included:

1. Location of the lesion (which spinal cord level)
2. Size of the lesion (in terms of how many vertebral segments)
3. Whether gadolinium injection was used and if so, was enhancement seen

During the trial period, the study team were able to request anonymized patients scans to be provided on a CD to resolve potential clinical and radiological uncertainties.

## **9.8 Analysis**

A comprehensive statistical analysis plan was developed and descriptive analysis (e.g. summary statistics and plots) was to be performed to investigate the distribution of the primary outcome, ASIA Impairment Scale score, across participants.

### **9.8.1 Statistical Analysis**

All analyses were to be pragmatic and follow the intention to treat (ITT) principle, that is, patients will be analysed in the groups to which they were randomised irrespective of treatment amount or treatment quality received, utilising all available follow-up data from all randomised patients. Sensitivity analyses will be used to assess the robustness of conclusions to missing outcome data and to departures from randomised treatment.

An interim futility analysis was scheduled to be conducted after 52 patients had provided a response (26 on each treatment arm), the endpoint being a two-point change in the ASIA scale 6 months after randomisation; the results were to be assessed by the Data Monitoring Committee.

The final analysis of effectiveness was scheduled to be conducted once the trial database had closed, if the study continued to full recruitment. The Data Monitoring Committee were to collate effectiveness and safety data during the trial to inform their recommendations to the Trial Steering Committee. Main effects was planned to be summarised by intervention arm and assessment time point with associated 95% Confidence Intervals.

### 9.8.2 Primary and secondary outcome analysis

The main objective of the statistical analysis was to assess the effect of IVIG on the primary outcome, a two-point change from baseline on the ASIA classification (A-E) scale, at 6-months post randomisation.

The secondary clinical assessments (EDSS, continuous ASIA motor and sensory scales, SCI, Paediatric quality of life, EQ5D and CSRI), with repeated measurements was also going to be analysed within a linear mixed model framework, where generalisations of the linear mixed model will be utilised to allow for outcomes with non-normal data if necessary. Those measures with one follow up assessment were to be evaluated with a general linear model. The statistical modelling was designed to feature the outcome measure(s) as the dependent variable with corresponding baseline measure(s) (if applicable), stratification factors and treatment group featuring as covariates.

As descriptive analyses, recruitment rate, consent rate, loss to follow-up, departures from randomised treatment and the prevalence of serious adverse events (specifying deaths and ITU admissions), were to be reported at 3, 6 and 12-months post-randomisation and summarized by treatment arm over the course of the study. Chi-squared (Fisher's exact test) was to be used for categorical outcomes (e.g. serious adverse events and mortality).

All analyses were scheduled to be repeated considering age status (adult or child) and putative biological markers as moderators by interaction with treatment group (control or intervention), allowing estimates of treatment effect in the sub populations to be summarized.

Explanatory analyses to assess the efficacy of the treatment within NMO or idiopathic TM diagnosis by allowing for an interaction with treatment arm were to be carried out. The ICC of the sites would have been explored by allowing for site as random effect in the statistical modelling.

With regards to missing data in post treatment outcome variables that would have arisen as participants discontinue treatment or are lost to follow-up, regression analyses based on maximum likelihood and resulting inferences would be valid provided the missing data generating mechanism is missing at random (MAR), that is "missingness" is predicted only by variables that are included in the model, including earlier values of the outcome variable.

We aimed to empirically assess whether any baseline variables predict missingness and should this be the case we would condition on such variables by including them in the statistical model. Sensitivity analyses would have been used to assess the robustness of conclusions to missing outcome data and to departures from randomised treatment as previously described by White *et al*, 2011.<sup>22</sup>

### 9.8.3 Futility analysis

As previously mentioned, an interim futility analysis was scheduled to be conducted after 52 patients had provided a response, 26 on each treatment arm, with the endpoint being a two-point change in the ASIA scale at 6 months. The trial would have been terminated with the conclusion that the new treatment is no better than standard if, based on these 52 patients, the test statistic is less than zero. If sample sizes were equal, this would occur if the successes under new treatment were fewer than under standard. Otherwise, the trial would proceed to the full sample size of 170. The SAS program two stage - interim - chi evaluates the design deleting outcomes that would correspond to futility. The tail probabilities under the null and alternative were 0.0228 and 0.8946. The inclusion of the futility analysis therefore represented a very small loss of power.

The SAS program two stage - stage1 - chi evaluates the properties of the first stage of the design. It showed that the probability of abandoning the study at the interim analysis is 0.4449 under the null and 0.0201 under the alternative. Thus, there was a good chance of stopping for futility when the treatments were equivalent and a very small chance when the desired treatment effect was present (see **Appendix 4** for Futility Analysis Plan).

### 9.8.4 Health economic analysis

The study team aimed to develop a health economic module structure and complete a write up of its economic analysis, within the 12 months following the end of patient data collection (i.e. 42 – 54 months from the start date).

Drug pricing data and primary care, secondary care and social care costs will be calculated as previously described. Costs will be combined with the primary outcome measure in the form of a cost-effectiveness analysis. If IVIG results in higher costs and better outcome, then an incremental cost-effectiveness ratio will be generated to show the extra cost incurred to achieve an extra unit of improvement. Owing to the uncertainty around results, cost-

effectiveness planes and cost-effectiveness acceptability curves will be used, with bootstrapping of skewed results.

Long-term cost-effectiveness over 5-year and 10-year periods will be calculated using a Markov model. Response to treatment will be classified, and transition probabilities between groups will be derived from 6-month and 12-month follow-up data. Costs and QALYs for each category will be derived from the trial data. As limited data will be available on long-term costs, we will conduct both deterministic and probabilistic sensitivity analyses.

All causes of withdrawal from randomised treatment will be reported.  $\chi^2$  (Fisher's exact test) will be used for categorical outcomes (eg, serious adverse events and mortality).

There will be missing data in post-treatment outcome variables as participants discontinue treatment or are lost to follow-up. Inferences will be valid provided the missing data generating mechanism is missing at random (MAR), and is not predicted by any variables in the model, that is, missingness is predicted only by variables that are included in the model.

The use of IVIG, IVMP, additional treatments and rescue PLEX will be recorded throughout the follow-up period and costed using drug pricing data from the British National Formulary and the Department of Health. Use of primary care, secondary care and social care will be recorded at three-month, 6-month and 12-month follow-ups using the CSRI, and costs calculated to determine total cost for THE control and treatment arms.

A cost-effectiveness analysis will be performed using the primary and secondary outcome measures of improvement in ASIA scores, and secondary outcome of QALYs with EQ-5D-Y, EQ-5D-5L and CSRI. If IVIG results in higher costs and better outcome, then an incremental cost-effectiveness ratio will be generated to show the extra cost incurred to achieve an extra unit of improvement.

## **9.9 Ethics and approvals**

This study is registered with EudraCT (REF: 2014-002335-34), Clinicaltrials.gov (REF: NCT02398994) and ISRCTN (REF: 12127581). Research Ethics Committee approval was obtained (South Central—Berkshire B; REC 14/SC/1329); alongside MHRA notification.

## 10 Trial outcome and results

Over the 53 weeks of recruitment, 26 potential participants were screened for eligibility across all 15 sites. Of these 26 participants, 24 were not randomised [ineligible (n=23, with 48% of these (11 of 23) too mild for inclusion and the remaining 52% (12 of 23) ineligible as they do not meet other inclusion or meet the exclusion criteria); and delay in referral of patient to PI (n=1)]. Two participants recruited into the study (**Figure 2**). One participant each was randomised to each arm of the trial, with each participant followed up for six months post randomisation prior to withdrawal from the study. This data is summarised in the CONSORT diagram (**Figure 2**). The number of participants randomised into the study was significantly below the target sample size, thus precluding any form of data analysis and detection of significant difference between the control and treatment arms of the study.

### 10.1 Baseline and three-month data summary

Descriptive summarisation of both participants' data was carried out following a lock of the study data, and the trial statistical team remained masked to treatment allocation up to this point. One was a white female child, aged between 10 and 15, a student with unknown BMI. This participant had an ASIA impairment score of C prior to randomisation, meaning that motor function is preserved below the neurological level and more than half the key muscles below this level have muscle grade less than 3. At 3-months post randomisation this participant had improved to ASIA impairment score of D meaning that at least half of the key muscle functions below the neurological level have a muscle grade of 3 or above. The other participant was a white adult male, aged between 60 and 65, in full-time employment with a BMI of 30. This participant had an ASIA impairment score of A prior to randomisation, meaning that no motor or sensory function is preserved in sacral segments S4 to S5. At 3 months post randomisation, this participant had not improved. Neither participant suffered a relapse during the trial. The adult participant suffered from two adverse events during the trial, a chest infection and pressure sores, which were not related to the trial, the paediatric participant suffered no adverse events. Due to the very small sample size it is not possible to comment on whether there is any relationship between the trial arm and any change in ASIA impairment scores.

## **10.2 Withdrawal**

Both randomised patients remained on the trial until their second follow-up visit (6-months post randomisation), at which point they were withdrawn from the study by the study team.

The rationale behind the termination and subsequent withdrawal were explained to both participants, both of whom have recourse to further information.

## **10.3 Health economics analysis**

As the trial did not recruit to a sufficient number, analysis of the health economic impact was not possible.

## **10.4 Investigator (opinion leader) feedback**

Following the termination of the study, the study team developed a survey that sought to both gain feedback on the study, as well as develop a better understanding of the reason, in the opinion of the investigator, the study did not recruit to target. The survey questions were sent to 13 of the 15 recruiting sites, as the remaining two sites were those of the chief investigator and the co-investigator/ Project co-ordinator, both of whom were involved in the design of the survey. Of the 13 investigators contacted, 11 responses were received. A summary of these responses are detailed in **Table 2**.

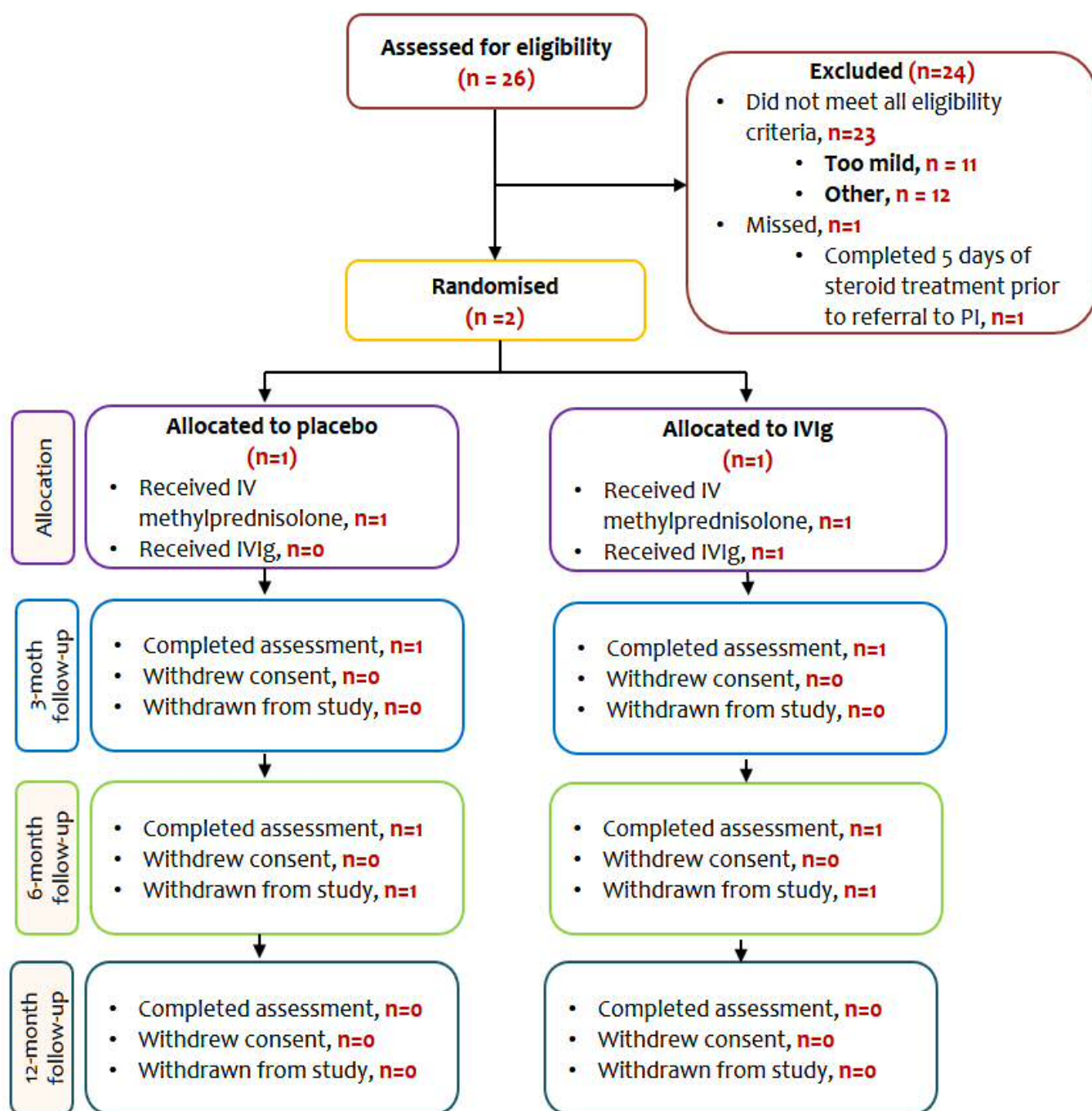


Figure 2. The Consolidated Standards of Reporting Trials (CONSORT) flow diagram.



**Table 2. Summary of the post-study survey of sites that took part in the STRIVE study**

Question	Investigator response ( <i>n</i> = 11)		
	Agree	Neither agree nor disagree	Disagree
1. The aim and overall objective of the study was clear	11	0	0
2. The study design was simple enough to understand	10	1	0
3. All the study procedures (including study visits at 3m, 6m and 12 months' post treatment) were in line with our standard care for TM/NMO patients	6	3	2
4. ASIA score was an appropriate outcome measure that could have been used	3	4	4
5. The trial offered a good treatment option for TM/NMO	7	3	0
6. The trial was sufficiently pragmatic	6	2	1
7. This site was an appropriate choice for STRIVE	11	0	0
8. I think addressing the study question is highly important and should be a priority	10	1	0
9. The outcome of this study would have changed how I treat my TM patients	9	1	1
10. Within my daily workload, I believe I had enough time to allocate to activities the study required (both clinical and administrative)	2	2	7
11. I generally find it difficult to do all kinds of clinical trials nowadays due to lack of time	7	3	1

	Investigator response (n = 11)		
Question	Agree	Neither agree nor disagree	Disagree
12. A STRIVE study visit by a participant had (or would have had) an undesirable impact on my clinic (e.g. significantly increasing length of clinic time or administration of clinic etc.)	5	3	3
13. I generally find it difficult to find time for all study visits nowadays	4	4	3
14. I was actively involved in the site feasibility discussion before the study opened at my site	8	2	0
15. Setup of the STRIVE study felt complicated at times	5	1	4
16. All things considered, I think funding for sites for this study was not really adequate	7	2	2
17. The study coordinating team could have done more to increase awareness of the study among other clinicians or potential patient population	4	1	6

	Strict inclusion criteria	No cases came to my attention	Came to know late of case	Did not have time	Other
18. I was unable to recruit because (as many as applicable):	9	5	7	0	1

<b>19.</b> What alternative to ASIA would you have considered if any?	Motor component of ASIA, EDSS, MSFC, assessment of mobility, a bespoke assessment score validated in advance
<b>20.</b> What in your opinion was the single most important reason this trial failed?	Strict inclusion criteria, rarity of cases, choice of outcome measure, early recognition of cases and finding time to recruit patients
<b>21.</b> What would you have changed about the study	Broader eligibility criteria, inclusion of less severe patients, use of different outcome assessment, improved awareness among all neurologist and engaging all sites earlier

## **11 Discussion: Lessons learnt from early closure of the trial**

The STRIVE study aimed to elucidate the added benefit in clinical efficacy and health economics associated with additional and early treatment of TM with IVIG when compared to the current standard therapy of IV steroids. Owing to the fact that the study under recruited, the study is unable to detect these difference. Nevertheless, the barriers encountered during the course of the trial are herein discussed. Other researchers planning a similar study would benefit from being aware of these barriers and its potential impact.

### **11.1 Overview of the trial evolution**

The first STRIVE recruiting site received the green light to start recruiting on 04/03/2015, while the final site to receive its approval did so on 08/02/2016. At the point of the study suspension (11/03/2016), 15 sites were open to recruitment, with two sites each recruiting one subject. The Trial Steering Committee (TSC) met on 11/03/2106, where strategies to further improve recruitment into the study was extensively discussed. Following this meeting, the TSC and Trial Management Group (TMG) jointly decided that further recruitment into the study should be suspended with immediate effect. The TSC and TMG came to this decision because the study, on its current trajectory, was unlikely to recruit to sufficient numbers as to allow scientifically valid deductions to be made. The study coordinating team consulted the National Institute for Health Research (NIHR) monitoring team and following further discussion with the respective programme directors, early termination of the study was agreed upon.

### **11.2 The need for better understanding of TM epidemiology**

A lower than expected frequency of patient encounters is believed to be the main factor that led to the low levels of recruitment observed in this study. The challenges associated with recruitment into rare disease trials are not restricted to this study alone. A large scale comparison of interventional trials (24,088 trials) of which 2,759 (11.5%) were classified as rare disease trials and 21,329 (88.5%) non-rare conditions found that rare disease trials are more likely to be terminated early (13.7%) compared to non-rare disease trials (6.3%).<sup>23</sup> The same study found that on average, the proportion of the actual number of patients recruited into a study compared to initial estimate is less for rare disease trials (70.1%)

compared to trials of non-rare conditions (81.6%). It is perhaps intuitively understandably that due to the uncommon nature of the disorder under study, one of the most frequent problem faced during the conduct of a rare disease trial is recruitment of the requisite number of study subjects.<sup>23,24</sup>

The trial team were aware of the challenges associated with recruitment into rare disease trials and prior feasibility assessment suggested a higher frequency of patient encounter than was eventually observed. With the yearly incidence of TM being approximately 350 (105 proportionately across the 15 open sites; based on study team projection that 24 sites would capture 50% of cases on TM in UK), the relatively low rate of patient encounter reported by all sites was unexpected. Furthermore, based on our estimated 35% recruitment rate, approximately 36 subjects could theoretically have been recruited by the open sites per year, against the two actually recruited. Interestingly, although numerous evidence (screening log, informal discussions with recruiting site personnel and the investigator survey response) point towards a low rate of patient encounter, anonymised data provided by the transverse myelitis patient group, Transverse Myelitis society (TMS), showed that approximately 61 registered members of their society (of whom 57 had a confirmed TM diagnosis) reported to having been diagnosed with TM in 2015 (**Appendix 5**). This data suggests that the incidence of the disease may not have been overestimated by the study team, especially as the TM society data is likely to be an underestimate of the true incidence of TM (it only reflects individuals that actually took time to register with the society). However, analysis of the geographical distribution of these subjects indicated that more than half of these patients were more than 25 miles away from each of the recruiting sites (**Appendix 5**). This observation points towards a level of geographical disconnect between the potential patients and the STRIVE sites. Additionally, although local TM cases were often referred to, or had their treatment discussed with the investigators involved in the STRIVE study, it likely that some potentially eligible subjects were seen and treated exclusively by their local physician. The study team took steps to ensure wide dissemination of the study among the neurology network by inclusion of the study in the Association of British Neurosciences newsletter and conferences, with email to members, presentation of the study at the TM society annual general meeting and conference, distribution of ward

leaflets and admission unit posters at participating sites and provision of study flyers for use in district general hospitals.

The low frequency of patient encounters was further complicated by the fact that a significant proportion of subjects that were considered for the trial were not eligible for inclusion into the study. One reason for this may be that investigators may not have wholly appreciated the strictness of the eligibility criteria during the feasibility assessment. Indeed “strict inclusion criteria” was cited by 82% (9 of 11) of respondents in the post-trial survey as a key factor they believe inhibited recruitment into the study. Notably these inclusion criteria were mandated by the primary endpoint of the study to be able to recruit patients of at least an ASIA impairment scale C to observe at least a 2-point improvement in this scale (*see Section 11.4*) This highlights the absolute necessity for further studies to establish a reflection of both the incidence, and equally as important, the severity of TM cases that are observed.

### **11.3 Navigating operational barriers in setup and running of a rare disease trial**

Although the low frequency of patient encounters primarily led to the study under recruiting, other barriers played an important role in complicating the study setup and running, and ultimately in the recruitment of subjects into the study. Hurdles in setting up the trial within the NHS sites, including contract and cost negotiation, local governance and a lack of capacity of research staff (research nurses and/or investigators’ competing priorities i.e. clinical and trial commitments) led to staggered opening of target sites. The overall impact of this is that at the time of the study closure, only 62.5% (15/24) of target sites were opened and recruiting. As recruitment logs were not available sites that failed to open (nine) the impact of the study may only be extrapolated. The impact of this is best understood in light of the fact that the 24 originally targeted sites were assumed to represent the neurology services that catered for approximately half of the UK population. With only 15 of these target sites open, approximately 31% of new TM/NMO cases were thus geographically covered.

Lack of research capacity, described as unavailability of site research staff or co-investigator, or competing clinical priorities and commitments to other trials, played a significant role in

five (5) of the initially 24 target sites failing to open. Unsurprisingly, in the survey of investigators that took part in this study, 63.6% (7 of 11) of investigators found it difficult to run all kinds of clinical trials at the present time due to lack of time. 27.3% (3 of 11) found it neither difficult nor easy, whilst one investigator (9.1%) did not currently find it difficult to run clinical trials due to lack of time.

The protracted contract negotiation and cost allocation highlights a wider issue of the differences in health service provision within different regions, in particular the interpretation of standard of care across different (neurology) services. For instance, whilst the premise of the study (which informed the funding structure) was that most of the study activities were within standard patient care, some of these activities, such as ASIA assessment, was evidently not routinely used within different neurological services. These differences impacted not only on the ability of target sites to be opened, but also how and when the site could be authorised to commence patient recruitment. Since site activation was predicated on at least one researcher within a site being ASIA trained, sites that did not routinely use this assessment tool would require a member of the research team (preferentially the principle investigator) to undertake the training and gain competence in ASIA assessment. Moreover, competency in ASIA assessment required an online training that may last up to 6 hours. At least one site remained unopened at the point of the study closure despite having all other approvals in place and having already had their site initiation visit. This site remained unopened as the PI was unable to complete the ASIA training up to the point of the study closure.

When considering these operational barriers, it is not immediately apparent how best to overcome these barriers associated with research capacity. Investigators, especially research active ones, are likely to routinely balance clinical activities with both their existing and new portfolio of clinical trials; whilst R&D departments balance the low cost effectiveness in initiating rare disease trial with high throughput or commercial studies. Ultimately, fiscal remunerations for adopting very rare disease trials are likely to be required to facilitate running of very rare disease trials with such barriers.

#### **11.4 Considerations of the design of the study**

Whilst the paucity of patient encounters and other operational barriers played a significant role in the study under recruiting, the contributory effect of the study design (in terms of eligibility criteria) to the under recruitment of the study cannot be overlooked. Analysis of site screening logs and feedback from investigators indicated the exclusion of “less severe” (i.e. patient with ASIA impairment score of D) patients had some impact on recruitment of patients into the study. Approximately 48% (11 of 23) of screened patients that did not meet the eligibility criteria was as a result of their symptoms being ‘mild’ or assessed as ASIA impairment scale D. The study team recognised this trend whilst the study was still active and considered amendment of the protocol to allow inclusion of patients assessed ASIA D or those whose symptoms were considered to be ‘mild’ at the time presentation. However, the primary endpoint of the study required patients to be of at least an ASIA impairment scale C to observe the 2-point improvement in this scale.

The short window for recruitment (5 days from the date of first commencement of steroid therapy) was the second factor identified to contributed to low recruitment. Whilst it would have been easy to remove this restriction, the early treatment paradigm was key to the study question and was deemed by study team to be important to retain.

#### **11.5 Achievements of STRIVE**

The barriers described individually above, and summarised in the STRIVE timeline on **Figure 3**, collectively contributed to a formidable barrier that prevented the study from maintaining steady momentum and recruiting to target. Nevertheless, despite the early termination of the study, the efforts in trying to run this trial has resulted in 2 major hidden rewards. Firstly, the study team has established a network of investigators comprising of both adult and paediatric neurologists who are ready to collaborate in future studies and clinical trials in TM and other neuroinflammatory conditions. Secondly, the study set-up has also provided key important training to the local investigator in evaluating patients with TM. As such, we now have 15 paediatric and adult neurology centres that is more equipped to manage adults and children with TM.



## **11.6 Conclusion and recommendations**

With 91% (10 of 11) of the STRIVE investigators (opinion leaders) surveyed agreeing that the study question is important and should be a priority, and 82% (9 of 11) of these noting that the outcome of the study would have changed how they treat TM patients, it is clear that this remains a pertinent question.

However, a future TM intervention trial design would benefit from having a robust, up-to-date information on incidence and distribution of severity of patients presenting with TM. Multi-source incidence studies in both adults and children within the intended intervention study population will negate need to extrapolate data. Such a trial must also accommodate the evidence accrued on the spectrum of severity within patients; and thus an alternative outcome measure is required beyond the ASIA impairment scale. Here, prospective studies recruiting patients to carefully evaluate the utility of other available measures, such as the ASIA motor score will be required. Importantly, lessons learnt from STRIVE, are easily applicable to other very rare disorders.

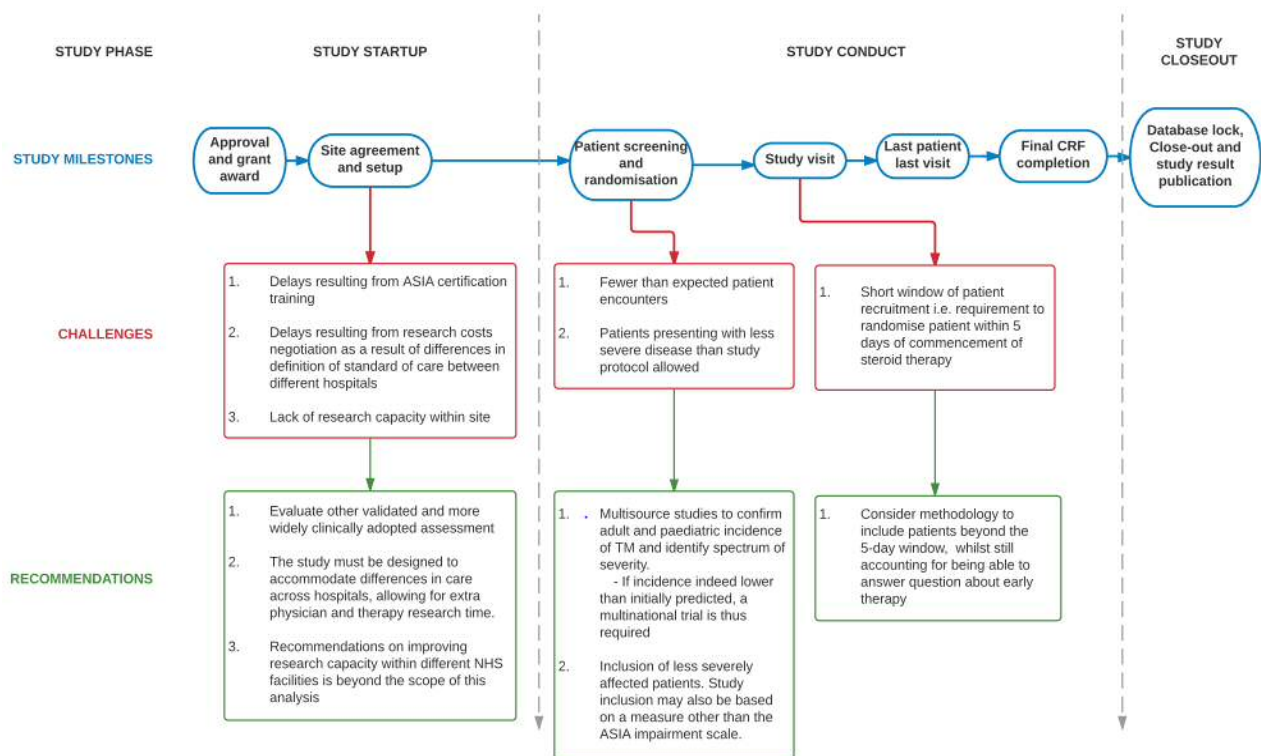


Figure 3. A summary of some of the barriers encountered during the conduct of the STRIVE study

## **12 Patient and public involvement**

Patient and public representatives were actively involved in the design of the research, management of the research and development of the participant information resources.

Transverse myelitis society, Multiple sclerosis society and Guthy-Jackson charitable foundation were involved in the design of the research. Two members from the TM society served on the Trial Steering Committee of the study. Their involvement was crucial in both finalising the research protocol and patient information sheet, as well as in the overall direction the study took. Additionally, they provided a lay perspective on the likely public perceptions of the study and offered key advice on how to maximise recruitment.

### 13 Acknowledgements

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All key data are included as an appendix to the report, and any further data desired but not listed there can be obtained from the corresponding author.

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## 15 References

1. Kerr DA, Ayetey H. Immunopathogenesis of acute transverse myelitis. *Curr Opin Neurol*. 2002 Jun;15(3):339–47.
2. Borchers AT, Gershwin ME. Transverse myelitis. *Autoimmun Rev*. 2012 Jan;11(3):231–48.
3. Transverse Myelitis Consortium Working Group. Proposed diagnostic criteria and nosology of acute transverse myelitis. *Neurology*. 2002 Aug 27;59(4):499–505.
4. Jacob A, McKeon A, Nakashima I, Sato DK, Elson L, Fujihara K, et al. Current concept of neuromyelitis optica (NMO) and NMO spectrum disorders. *J Neurol Neurosurg Psychiatry*. 2013 Aug;84(8):922–30.
5. Altrocchi PH. ACUTE TRANSVERSE MYELOPATHY. *Arch Neurol*. 1963 Aug;9:111–9.
6. Kaplin AI, Krishnan C, Deshpande DM, Pardo CA, Kerr DA. Diagnosis and management of acute myelopathies. *The Neurologist*. 2005 Jan;11(1):2–18.
7. de Seze J, Lanctin C, Lebrun C, Malikova I, Papeix C, Wiertlewski S, et al. Idiopathic acute transverse myelitis: application of the recent diagnostic criteria. *Neurology*. 2005 Dec 27;65(12):1950–3.
8. Absoud M, Lim M, Wassmer E . Chapter 7: Inflammatory, Metabolic, Vascular, and Demyelinating Disorders. In Michael Pike, editor. *Disorders of the Spinal Cord in Children Clinics in Developmental Medicine*. London:Mac Keith Press; 2013. pp. 152 – 185.
9. Young J, Quinn S, Hurrell M, Taylor B. Clinically isolated acute transverse myelitis: prognostic features and incidence. *Mult Scler Houndmills Basingstoke Engl*. 2009 Nov;15(11):1295–302.



10. Absoud M, Lim MJ, Chong WK, De Goede CG, Foster K, Gunny R, et al. Paediatric acquired demyelinating syndromes: incidence, clinical and magnetic resonance imaging features. *Mult Scler Houndmills Basingstoke Engl*. 2013 Jan;19(1):76–86.
11. Greenberg BM, Thomas KP, Krishnan C, Kaplin AI, Calabresi PA, Kerr DA. Idiopathic transverse myelitis: corticosteroids, plasma exchange, or cyclophosphamide. *Neurology*. 2007 May 8;68(19):1614–7.
12. Frohman EM, Wingerchuk DM. Clinical practice. Transverse myelitis. *N Engl J Med*. 2010 Aug 5;363(6):564–72.
13. Scott TF, Frohman EM, De Seze J, Gronseth GS, Weinshenker BG, Therapeutics and Technology Assessment Subcommittee of American Academy of Neurology. Evidence-based guideline: clinical evaluation and treatment of transverse myelitis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2011 Dec 13;77(24):2128–34.
14. Weinshenker BG, O'Brien PC, Petterson TM, Noseworthy JH, Lucchinetti CF, Dodick DW, et al. A randomized trial of plasma exchange in acute central nervous system inflammatory demyelinating disease. *Ann Neurol*. 1999 Dec;46(6):878–86.
15. Hughes RAC, Dalakas MC, Cornblath DR, Latov N, Weksler ME, Relkin N. Clinical applications of intravenous immunoglobulins in neurology. *Clin Exp Immunol*. 2009 Dec;158 Suppl 1:34–42.
16. Banwell B, Ghezzi A, Bar-Or A, Mikaeloff Y, Tardieu M. Multiple sclerosis in children: clinical diagnosis, therapeutic strategies, and future directions. *Lancet Neurol*. 2007 Oct;6(10):887–902.
17. Elson L, Panicker J, Mutch K, Boggild M, Appleton R, Jacob A. Role of intravenous immunoglobulin in the treatment of acute relapses of neuromyelitis optica: experience in 10 patients. *Mult Scler Houndmills Basingstoke Engl*. 2014 Apr;20(4):501–4.

18. Dalakas MC. Mechanism of action of intravenous immunoglobulin and therapeutic considerations in the treatment of autoimmune neurologic diseases. *Neurology*. 1998 Dec;51(6 Suppl 5):S2-8.
19. Awad A, Stuve O. Idiopathic Transverse Myelitis and Neuromyelitis Optica: Clinical Profiles, Pathophysiology and Therapeutic Choices. *Curr Neuroparmacol*. 2011 Sep 1;9(3):417–28.
20. Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG. Revised diagnostic criteria for neuromyelitis optica. *Neurology*. 2006 May 23;66(10):1485–9.
21. Absoud M, Gadian J, Hellier J, Brex PA, Ciccarelli O, Giovannoni G, et al. Protocol for a multicentre randomised controlled Trial of Intravenous immunoglobulin versus standard therapy for the treatment of transverse myelitis in adults and children (STRIVE). *BMJ Open*. 2015 May 25;5(5):e008312–e008312.
22. White IR, Horton NJ, Carpenter J, Pocock SJ. Strategy for intention to treat analysis in randomised trials with missing outcome data. *BMJ*. 2011 Feb 7;342(feb07 1):d40–d40.
23. Bell SA, Tudur Smith C. A comparison of interventional clinical trials in rare versus non-rare diseases: an analysis of ClinicalTrials.gov. *Orphanet J Rare Dis*. 2014;9:170.
24. Griggs RC, Batshaw M, Dunkle M, Gopal-Srivastava R, Kaye E, Krischer J, et al. Clinical research for rare disease: Opportunities, challenges, and solutions. *Mol Genet Metab*. 2009 Jan;96(1):20–6.

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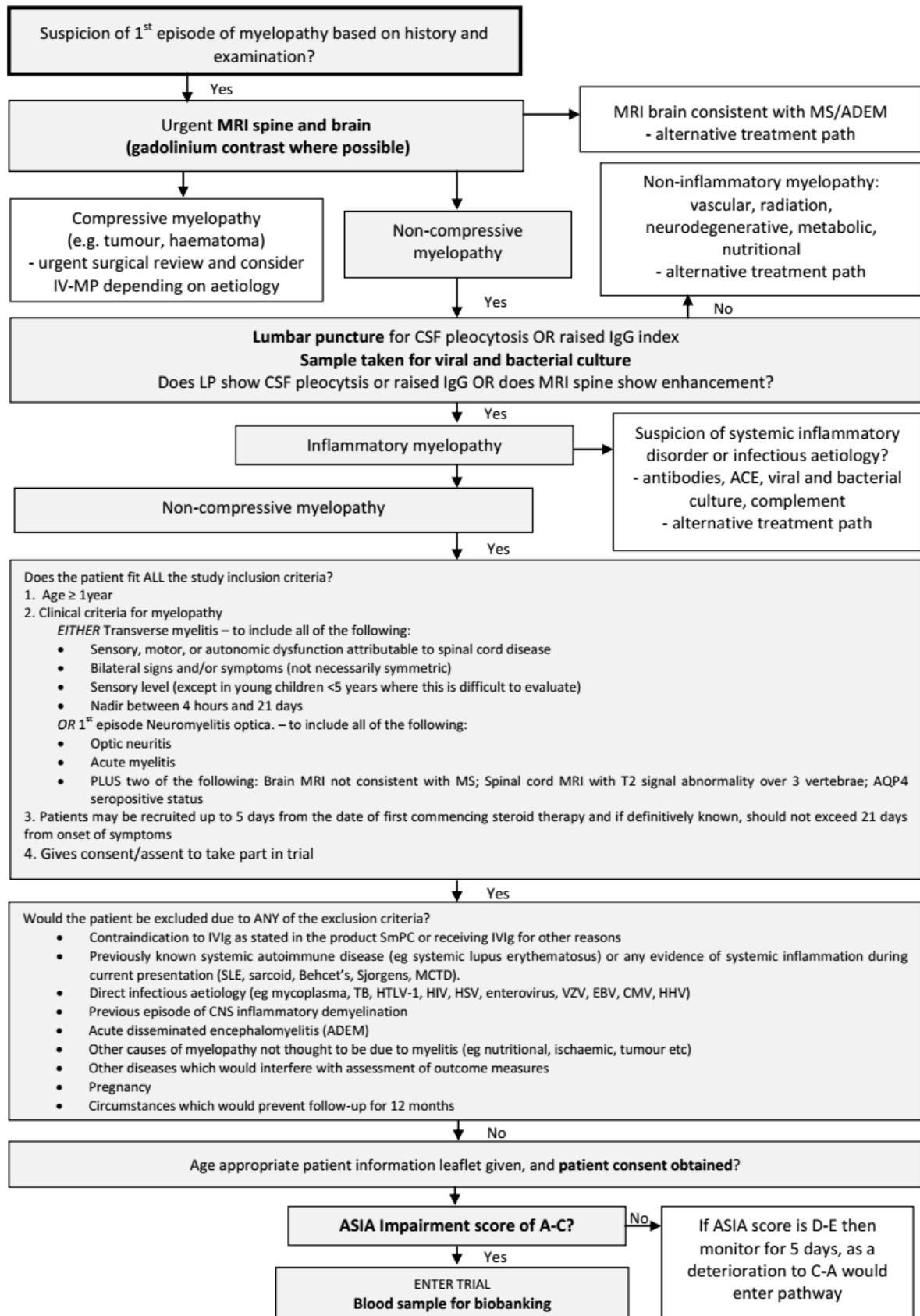
## 16 Appendices

### 16.1 Appendix 1: Dosing table for IVIG administration

Weight (kg)	Day 1 (g)	Day 2 (g)	Day 3 (g)	Day 4 (g)	Day 5 (g)	Actual dose (g)
5.0 - 6.2	5	5				10
6.3 - 8.7	10	5				15
8.8 - 11.2	10	10				20
11.3 - 13.7	15	10				25
13.8 - 16.2	20	10				30
16.3 - 18.7	20	15				35
18.8 - 21.2	20	20				40
21.3 - 23.7	25	20				45
23.8 - 26.2	30	20				50
26.3 - 28.7	30	25				55
28.8 - 31.2	30	30				60
31.3 - 33.7	35	30				65
33.8 - 36.2	40	30				70
36.3 - 38.7	40	35				75
38.8 - 41.2	40	40				80
41.3 - 43.7	20	20	20	15	10	85
43.8 - 46.2	20	20	20	20	10	90
46.3 - 48.7	20	20	20	20	15	95
48.8 - 51.2	20	20	20	20	20	100
51.3 - 53.7	25	20	20	20	20	105
53.8 - 56.2	30	20	20	20	20	110
56.3 - 58.7	30	25	20	20	20	115
58.8 - 61.2	30	30	20	20	20	120
61.3 - 63.7	30	30	25	20	20	125
63.8 - 66.2	30	30	30	20	20	130
66.3 - 68.7	30	30	30	25	20	135
68.8 - 71.2	30	30	30	30	20	140

Weight (kg)	Day 1 (g)	Day 2 (g)	Day 3 (g)	Day 4 (g)	Day 5 (g)	Actual dose (g)
71.3 - 73.7	30	30	30	30	25	145
73.8 - 76.2	30	30	30	30	30	150
76.3 - 78.7	35	30	30	30	30	155
78.8 - 81.2	40	30	30	30	30	160
81.3 - 83.7	40	35	30	30	30	165
83.8 - 86.2	40	40	30	30	30	170
86.3 - 88.7	40	40	35	30	30	175
88.8 - 91.2	40	40	40	30	30	180
91.3 - 93.7	40	40	40	35	30	185
93.8 - 96.2	40	40	40	40	30	190
96.3 - 98.7	40	40	40	40	35	195
98.8 - 101.2	40	40	40	40	40	200
101.3 - 103.7	45	40	40	40	40	205
103.8 - 106.2	50	40	40	40	40	210
106.3 - 108.7	50	45	40	40	40	215
108.8 - 111.2	50	50	40	40	40	220
111.3 - 113.7	50	50	45	40	40	225
113.8 - 116.2	50	50	50	40	40	230
116.3 - 118.7	50	50	50	45	40	235
118.8 - 121.2	50	50	50	50	40	240
121.3 - 123.7	50	50	50	50	45	245
123.8 - 126.2	50	50	50	50	50	250
126.3 - 128.7	55	50	50	50	50	255
128.8 - 131.2	60	50	50	50	50	260

## 16.2 Appendix 2: Clinico-radiological diagnostic algorithm



### **16.3 Appendix 3: Common side effects associated with Intratect™**

Intratect® can cause adverse reactions such as chills, headache, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and mild back pain, which may occur occasionally.

Rarely human normal immunoglobulins may cause a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration.

Cases of reversible aseptic meningitis, isolated cases of reversible haemolytic anaemia/haemolysis and rare cases of transient cutaneous reactions, have been observed with human normal immunoglobulin.

Increase in serum creatinine level and/or acute renal failure have been observed.

Very rarely: Thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, deep vein thrombosis.

Details of further spontaneously reported adverse reactions:

- Cardiac disorders: Angina pectoris (very rare)
- General disorders and administrations site conditions: Rigors (very rare)
- Immune system disorders: Anaphylactic shock (very rare), hypersensitivity (very rare)
- Investigations: Blood pressure decreased (very rare)
- Musculoskeletal and connective tissue disorders: Back pain (very rare)
- Respiratory, thoracic and mediastinal disorders: Dyspnoea NOS (very rare)
- Vascular disorders: Shock (very rare)

The adverse events reported above are expected, in the sense that they are possible known side effects of the study medication, but all reported instances of both serious and non-serious adverse events would be reported in this study. For a more detailed list of all reactions, refer to Intratect Summary of Product Characteristics (SmPC): <http://www.medicines.org.uk/emc/medicine/23175/SPC/intratect/>

## 16.4 Appendix 4: Futility analysis plan

### PROPOSAL FOR AN INTERIM FUTILITY ANALYSIS

#### 1. Introduction

Patients suffering from transverse myelitis will be randomised equally between IV immunoglobulin (the experimental arm: E) and steroids (the control arm: C). The primary analysis will concern response to treatment, defined as an improvement by two points on a paralysis assessment scale over a six-month period following treatment. It is anticipated that the success rate on C will be  $p_C = 0.5$ . The trial is to have 90% power to achieve significance at the 0.05 level (two-sided) if the success rate on E is  $p_E = 0.75$ .

The final analysis of the study can be conducted in terms of the statistic  $\chi^2 = \frac{2(O - E)^2}{E}$  which can be shown to be equal to  $Z^2/V$  where

\_\_\_\_\_

$p_C = p_E = 0.5$  and assuming that  $p_C = 0.5$ ;  $p_C = 0.75$ . The possible outcomes are then arranged in descending order according to  $T$ , and cumulative probabilities of  $T$  being  $\geq$  every possible value from 76 to -76 are computed. Reading the last row of the output for which

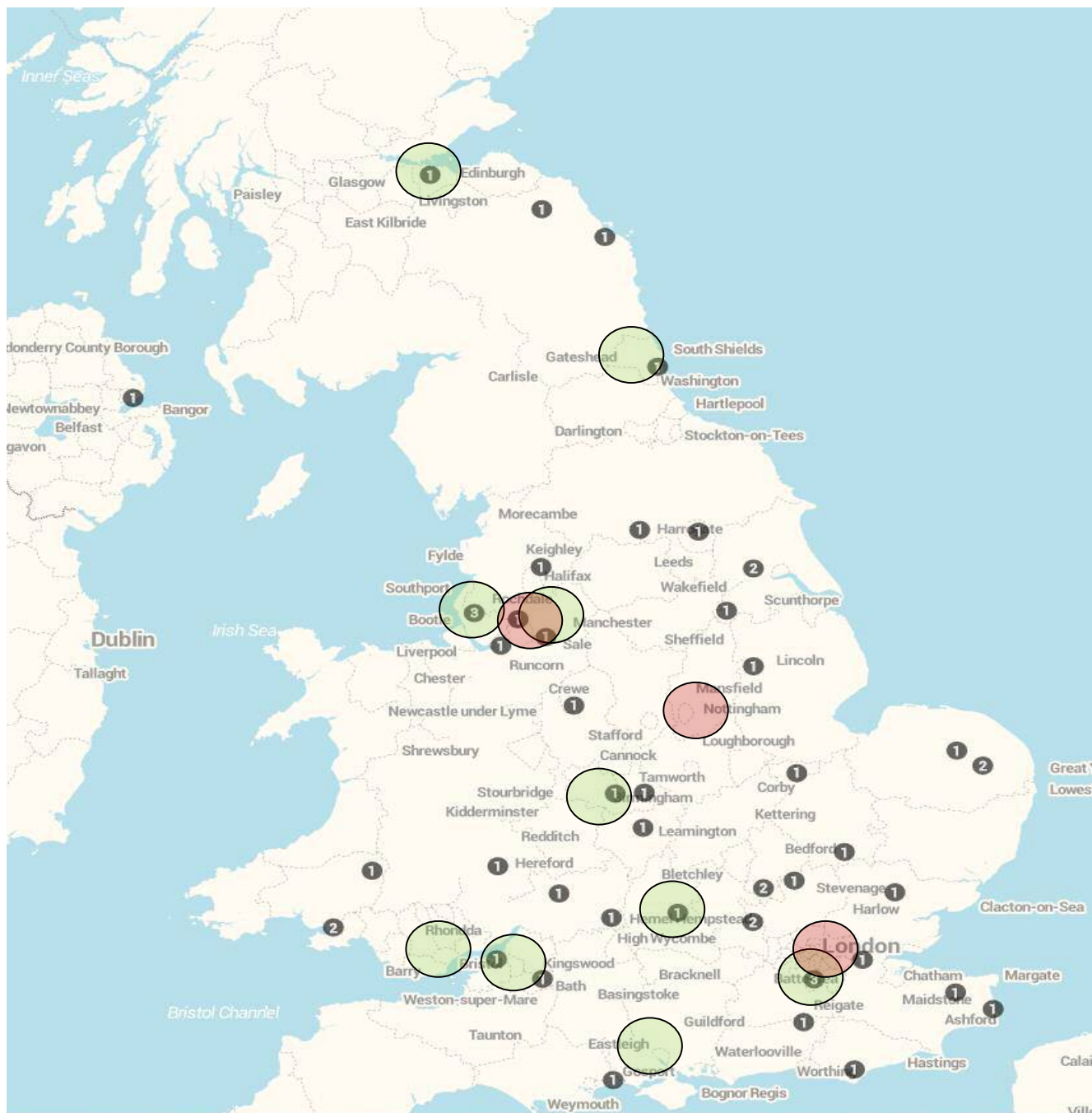


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Variations to the procedure, with different sample sizes at the interim and the null can be evaluated, and properties under different pairs of values  $p_C$  and  $p_E$  can be found. It would also be simple to investigate a more stringent futility criterion, requiring  $\hat{\theta}$  to exceed a value such as 0.5 or 1 in order to continue. This would make the loss of power more substantial, and open up the question of whether it should be compensated for by an increase in sample size.

Notice that no opportunity for stopping at the interim analysis due to strong evidence of efficacy is allowed. If that were allowed, then the properties of the method would need substantial re-evaluation and conventional analyses would no longer be conservative.

**16.5 Appendix 5: Geographical distribution of persons diagnosed with TM in 2015**  
**(as per Transverse Myelitis society data) in relation to STRIVE trial sites.**

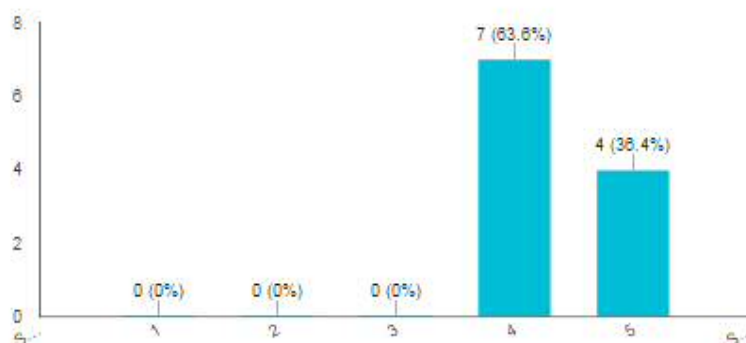


Where each numbered black sphere represents the number of individuals within the region on the map that reported (reported to TM society) to have been diagnosed with TM in 2015. Each green sphere represents a 25-mile radius around a STRIVE recruiting site, whilst the red spheres represent a 25-mile radius around STRIVE sites that were targeted for opening were the study not terminated.

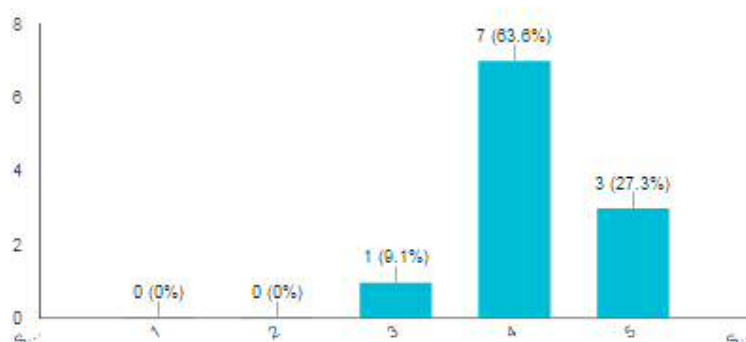
## 16.6 Appendix 6: Investigator responses to the post STRIVE trial survey

(1 = strongly disagree, 2 = disagree, 3 = neither agree nor disagree, 4 = agree, 5 = strongly agree)

### 1. The aim and overall objective of the study was clear (11 responses)

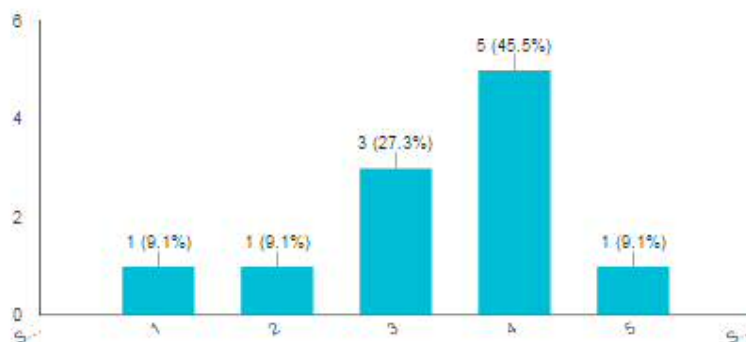


### 2. The study design was simple enough to understand (11 responses)



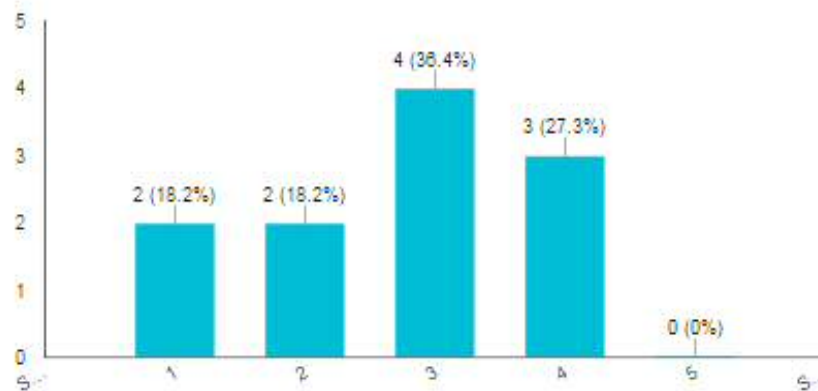
### 3. All the study procedures (including study visits at 3m, 6m and 12 months post treatment) were in line with our standard care for TM/NMO patients

(11 responses)



#### 4a. ASIA score was an appropriate outcome measure that could have been used

(11 responses)



#### 4b. What alternative would you have considered if any? (4 responses)

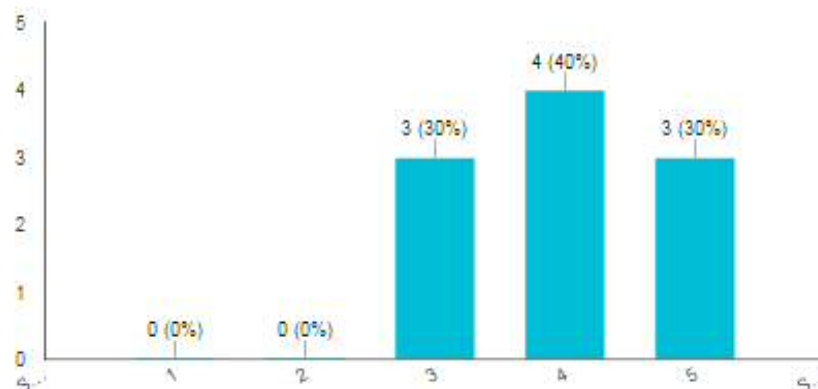
motor component of asia

EDSS, MSFC

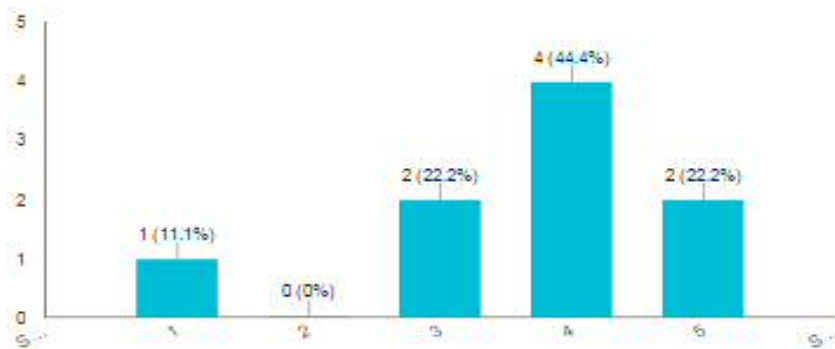
A new score should have been designed for the study and validated in advance. The score is inappropriate, gives useless functional information, the training is tedious and it is particularly useless for young children. The rectal exam is inappropriate for children. I'm sure this was one of the reasons the study failed.

EDSS, assessment of mobility - timed walk, single stick, 2 sticks, wheelchair

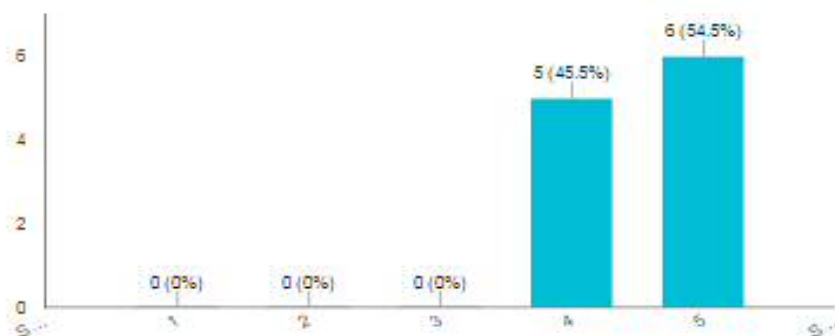
#### 5. The trial offered a good treatment option for TM/NMO (10 responses)



6. The trial was sufficiently pragmatic (9 responses)

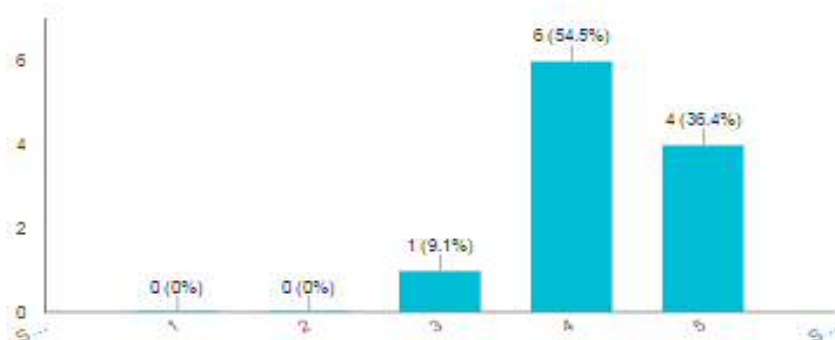


7. This site was an appropriate choice for STRIVE (11 responses)

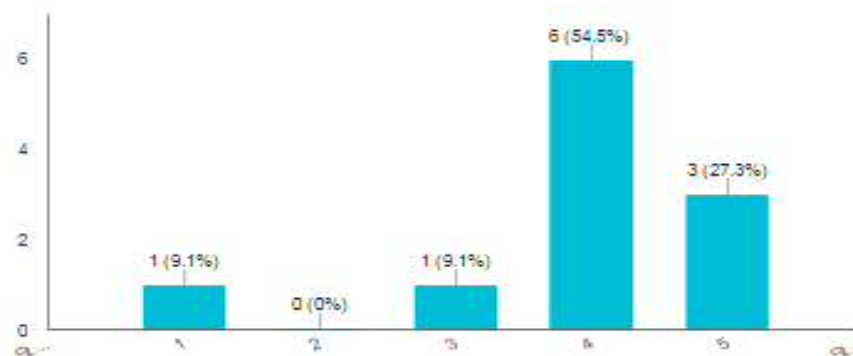


INVESTIGATOR

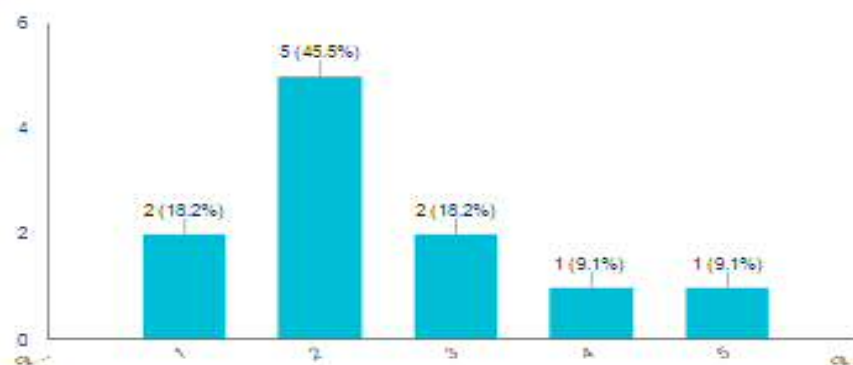
1. I think addressing the study question is highly important and should be a priority (11 responses)



2. The outcome of this study would have changed how I treat my TM patients  
(11 responses)



3. Within my daily workload, I believe I had enough time to allocate to activities the study required (both clinical and administrative)  
(11 responses)

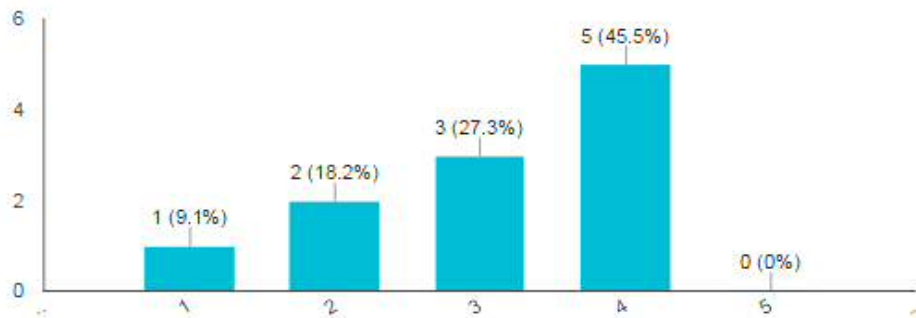


4. I generally find it difficult to do all kinds of clinical trials nowadays due to lack of time  
(11 responses)



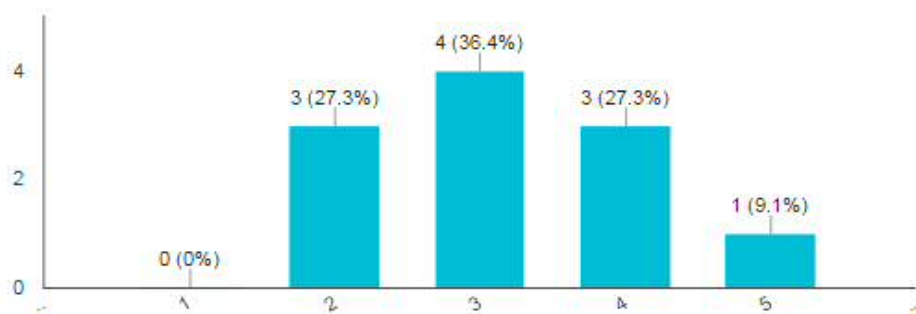
5. A STRIVE study visit by a participant had (or would have had) an undesirable impact on my clinic (e.g. significantly increasing length of clinic time or administration of clinic etc.)

(11 responses)



6. I generally find it difficult to find time for all study visits nowadays

(11 responses)







## 7. What in your opinion was the single most important reason this trial failed (important please answer)

(11 responses)

require too severe patients and excluded AQP4 ab pos patients

very constrained inclusion criteria

Early recognition and treatment of tm

Lack of appropriate patients available to recruit within the time window

rarity of cases, also Plasma exchange was my treatment of choice for severely affected patients

incidence overestimated. but also patients were being dxed earlier and started on steroids therefore most patients were mild disease ( not fitting inclusion criteria) and already on steroids for >5 days)

ASIA module tricky and few patients

Rarity of patients with severe enough weakness. Difficulty transporting in-patients to centre with required timescale

Choice of outcome measure

the rarity of severe transverse myelitis outwith MS simply made it difficult to find patients, and those we did identify were frequently too mildly affected to be eligible (or too mild for admission so by time seen in OP they were too late for study)

Finding time to recruit patients.

## 8. What would you have changed about the study (important please answer)

(11 responses)

broader eligibility criteria and far less optimistic estimate of numbers

extended and modified inclusion criteria and improved awareness amongst all neurologists

Broader screening/ recognition

Use patients with milder ASIA score as well?

ASIA was far too time consuming

inclusion criteria -to include milder patients and use ivig later than 5 days ie upto 10days from starting steroids

attempt to get all sites on board earlier- asia training at onset; site green light spread over too long

I would have lowered the severity of weakness needed for inclusion and adapted the ASIA score to make it easier to use.

see above

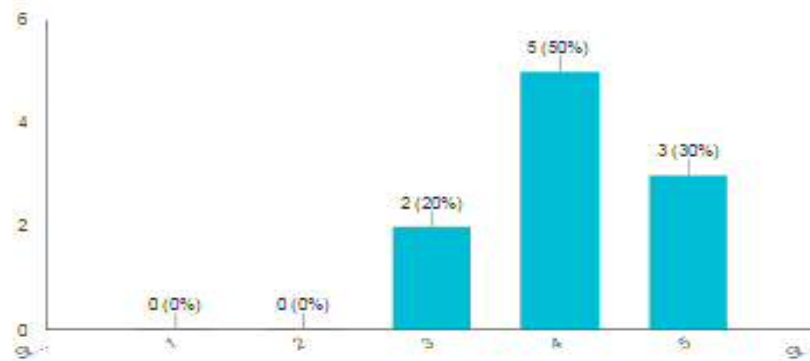
difficult – i'd have considered an alternative measure other than ASIA scale as most neurologists not familiar with this, but this didn't stop recruitment, the issue was identifying suitable patients. Not sure how to solve this other than having more study sites (?more paediatric especially) and longer period for recruitment, or potentially including milder TM patients.

A more user friendly assessment

## STUDY SETUP AND RECRUITMENT

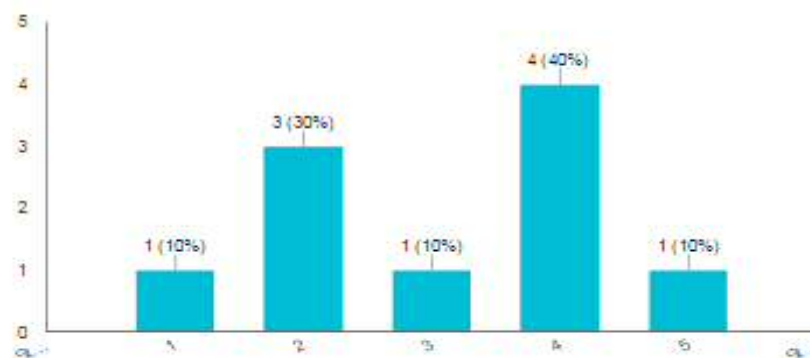
### 1. I was actively involved in the site feasibility discussion before the study opened at my site

(10 responses)



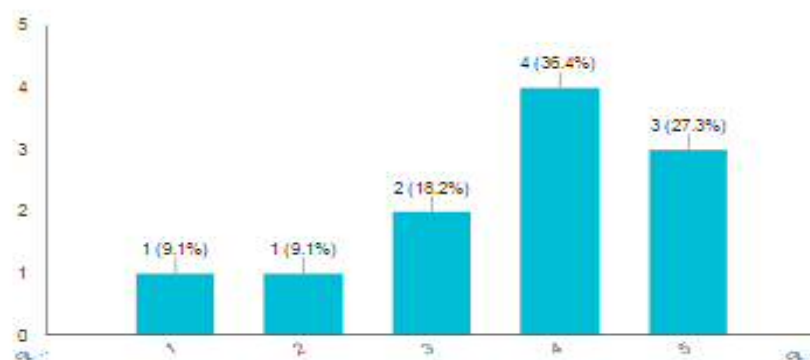
### 2. Setup of the STRIVE study felt complicated at times

(10 responses)



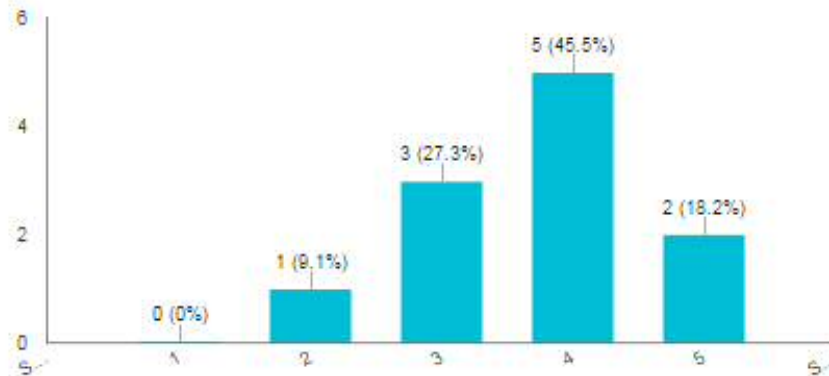
### 3. All things considered, I think funding for sites for this study was not really adequate

(11 responses)



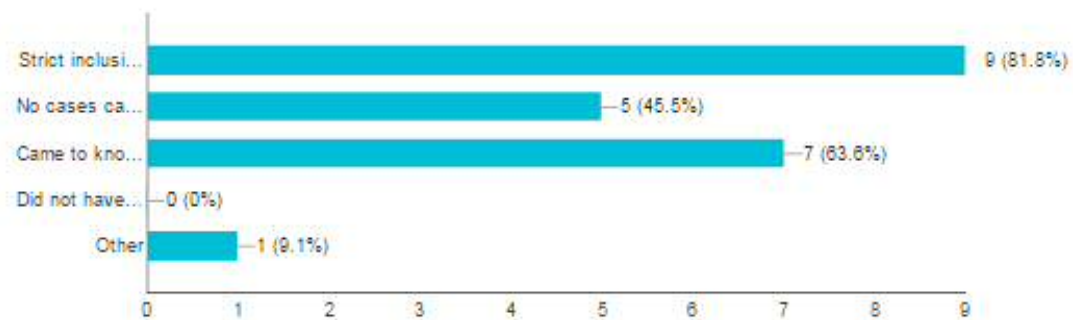
4. I found my interaction with our R&D department useful during the setup and administration of this study (if applicable)

(11 responses)



5. I was unable to recruit because (choose as many as applicable):

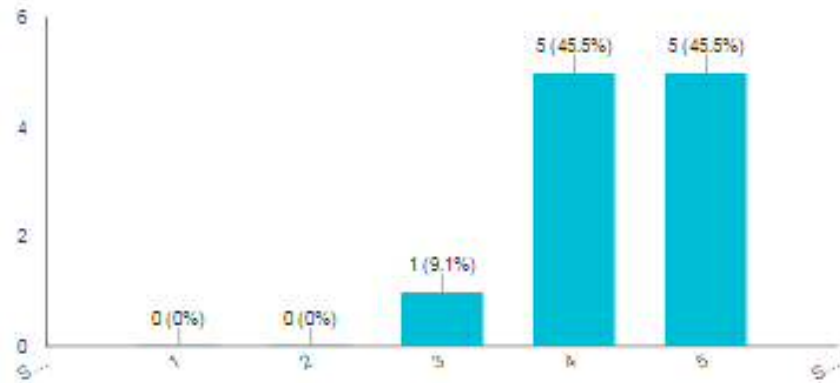
(11 responses)



## OTHER

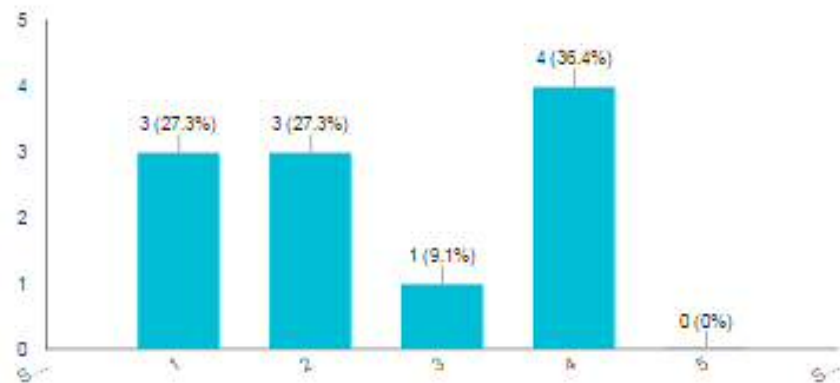
1. I received as much assistance as needed from the study coordinating team (Trial manager, sponsors etc.)

(11 responses)



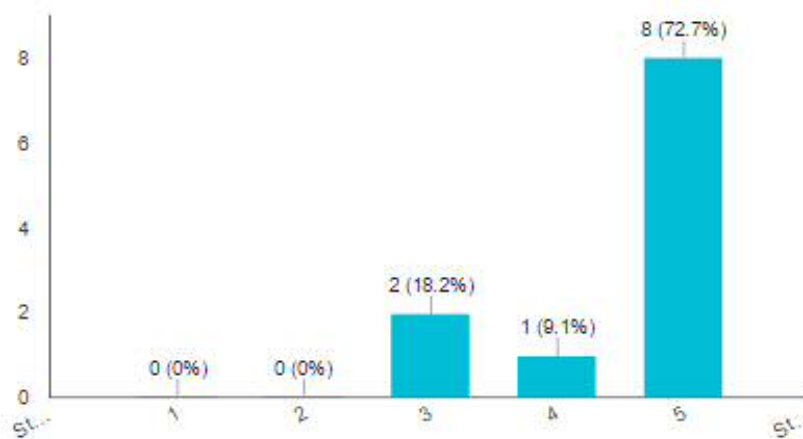
2. The study coordinating team could have done more to increase awareness of the study among other clinicians or potential patient population

(11 responses)



### 3. In future, I would be interested in collaborating with this team in designing and running another study

(11 responses)



### 4. Any other comments? Please feel free to be critical, as we would like to learn from this study any mistakes

(5 responses)

I said all along (as did others) that we would never get the numbers recruited (the leads assumed we would get 80% of all UK patients despite only a few sites involve let alone 89% being too high)  
Also the Kings team insisted on every team member being trained in everything despite not needed ie they made the study far more resource intensive than any pharma company and there was very little funds

this is good network of clinicians to run future studies

no

Is it possible to do a study to validate a simple, clinically useful score for the outcome of TM in children and adults which looks at functional outcome and is meaningful for the patients? Ask them what they think are useful outcomes

I thought the study team were very helpful but couldn't get round the fact that these cases are rare, especially outwith MS or established NMO, so will always be difficult to recruit i suspect.